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WHERE IS STREPTOMYCIN?

ALTHOUGH long heralded by the public press, streptomycin remains a promise of the future for pharmacists and most physicians. General distribution is probably many months away. The facts are that production facilities are still in the construction stage, and the scope and proper methods of streptomycin treatment are largely unknown.

Rapid developments can now be expected for this reason: Eleven pharmaceutical and chemical manufacturers are contributing more than a half million dollars to the National Research Council for a program of clinical studies to be administered by Dr. Chester S. Keefer, who did such an excellent job of the same type on penicillin. This should produce the greatest amount of clinical data in the shortest time with the expenditure of a minimum amount of material.

By this cooperative venture—and by sinking some $20,000,000 into production facilities for a drug that remains enigmatic profitwise—manufacturing pharmacists and chemists show a public-spirited interest in expediting therapeutic progress. That their investment may pay off later does not detract from the fact that these firms have the foresight and progressiveness to join in this first privately financed, nationally coordinated clinical evaluation in our history.

In the case of the penicillin program, finances and facilities were available through the Office of Scientific Research and Development, a wartime government agency about to be liquidated. In the case of streptomycin the way was open for incoordinated and overlapping clinical trials which surely would have prolonged the period of evaluation and would have led to sporadic and erratic distribution.

Despite past rumors, events have borne out our belief that penicillin products went to the retail pharmacist and community physician just as soon as they were evaluated and supplies seemed reasonably adequate. There is reason to believe that this same policy will be followed for streptomycin.

For the present, 37% of the available streptomycin has been allocated by the Civilian Production Administration (order M300-119) to civilian clinical research under Dr. Keefer. The remaining 63% will go to the Army, Navy, U. S. Public Health Service and Veterans' Administration. Total streptomycin production for March was about 27,000 Gm.

During the coming months many pharmacists will be receiving inquiries from patients and from their physicians regarding streptomycin. It should be clearly understood that the drug is not available from producers or government agencies. Inquirers should be advised that:

1. Streptomycin is available only for clinical trial until further notice.

2. All requests for the drug must be made of Dr. Chester S. Keefer, Evans Memorial Hospital, Boston, Mass. (telephone: Kenmore 9200).

3. Requests are to be submitted only by physicians, who should supply complete clinical data on their cases when applying and be willing to submit adequate records on the results of treatment.

4. Appeals for streptomycin should be restricted to infections that are not susceptible to the action of sulfonamides, penicillin or other therapeutic agents.

When sufficient clinical evidence has accumulated, Dr. Keefer will bring in a report on indications, contraindications, methods of administration and dosage. There is evidence that this new antibiotic will emerge as a prescription drug of major importance. Nevertheless, its therapeutic range of effectiveness will undoubtedly be far less than that of penicillin, and there have been disconcerting indications that drug fastness will constitute a problem.

STREPTOMYCIN PRODUCERS

Producers of streptomycin, constituting the Streptomycin Producers Advisory Committee of the Civilian Production Administration, who contributed in equal shares to the program of clinical evaluation:

ABBOTT LABORATORIES
COMMERCIAL SOLVENTS CORPORATION
CHARLES PFIZER & CO., INC.
E. R. SQUIBB & SONS
ELI LILLY & CO.
HEYDEN CHEMICAL CORPORATION
MERCK & CO., INC.
PARKE, DAVIS & CO.
SCHENLEY LABORATORIES, INC.
THE UPJOHN CO.
WYETH, INC.

REPRINTS OF JOURNAL PAPERS

Sirs:

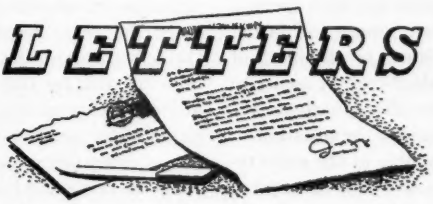
What is parachlorophenol and where may I obtain a supply?

Can I purchase reprints of articles in the JOURNAL for distribution to physicians? I find both editions of the JOURNAL extremely useful in keeping up with things in pharmacy.

Baltimore, Md. WILLIAM M. GOULD

Parachlorophenol is a disinfectant available from the Dow Chemical Co., Midland, Mich., the Monsanto Chemical Co., 1700 S. 2nd St., St. Louis 4 or Eastman Kodak Co., Rochester 4, N. Y. See page 160 for a new use of this chemical in conjunction with penicillin.

Reprints of JOURNAL *papers are often available either from the author or editorial office. Quantity orders which require a special printing must be received promptly after publication before the type is distributed. When reprints are unavailable some readers purchase a few extra copies of the* JOURNAL.—THE EDITOR.



PHARMACIST'S BASIC BOOKSHELF DISCUSSED

Sirs:

Being at home convalescing from a heart attack, I had plenty of time to digest the excellent article on a well-balanced basic library in the February issue. I pride myself on being one of the few bibliophiles in pharmacy, with one of the largest privately owned pharmaceutical libraries in the U. S. including books in many languages. To my great surprise and sorrow I find two kinds of books not mentioned in your basic list: pharmaceutical history and synonyms.

What books have I to suggest? In history, which should be represented in every pharmaceutical library, four outstanding volumes are *Geschichte der Pharmazie* by H. Schelenz (a master work but out of print, I believe), *Chronicles of Pharmacy* by Wootton, *Four Thousand Years of Pharmacy* by LaWall, and last but not least, *History of Pharmacy* by Kremers and Urdang.

The best single volumé on synonyms, which we use so often it is coming apart, is *Manual International Pharmacy* by A. Graa. One may readily find synonyms for a given drug title in Latin, English, German, French or Italian. . . . Graa was a well-educated, Swiss-born pharmacist, living in New York City, who mastered all 5 languages. The book was his life work. When he discovered how few pharmacists would buy it at $4 he became thoroughly disgusted and returned to Switzerland. The surplus printed pages were sold as old paper. Consequently the book is unobtainable today.

During my European tour in 1926, when I helped found the *Geselschaft fuer Geschichte der Pharmazie*, I was fortunate to locate Graa in Basel and had him as my guest at the hotel. He still had a grudge against pharmacy in the United States. . . .

Permit me to point out the routine followed in my two establishments when we get a prescription or a call for a formula, drug or herb with which we are not familiar. . . . The following books are consulted in rotation: (*a*) U. S. P., (*b*) N. F., (*c*) A. PH. A. Pharmaceutical Recipe Book, (*d*) U. S. Dispensatory; then if necessary we go to some special book. In the case of a German, French or Italian title we consult Graa; Spanish or Portuguese — *Memorandum Synonimias*, which one of my friends sent me from Madrid; French formulas—*Dorvault L'-Officine;* Italian—*Orosi Farmacologica;* British—*Pharmaceutical Codex* and *Extra Pharmacopoeia;* German and also other continental formulas—*Hager's Pharmazeutische Praxis*. . . .

Brooklyn, N. Y. OTTO RAUBENHEIMER

Sirs:

The recent article, "A Well-Balanced Basic Library," should provoke some of us who have been out of college for quite a while—twenty years in my case—to check up on our library to see if we are letting things slip a bit.

While my prescription practice is not large I like to give it the best I can, so please send me the enclosed list of books.

Phelps, N. Y. W. J. WHITSON

Sirs:

The suggestions for the pharmacist's basic bookshelf in the February issue of the PRACTICAL PHARMACY EDITION were very inclusive except for dentistry. One of the musts that should have been included is *Accepted Dental Remedies.* A general textbook on dental pharmacology and therapeutics would also be useful.

. . . A better comprehension of dentistry and dental needs would make for a better understanding between our two health professions.

University of Maryland EDWARD C. DOBBS
Dental School

Dr. Dobbs' point is well taken. Accepted Dental Remedies (*$1.50*) *is published annually by the American Dental Association, 222 E. Superior St., Chicago 11. Also to be recommended is* Pharmacology and Dental Therapeutics (*$6.50*) *by Prinz, Rickert and Dobbs; C. V. Mosby Co., St. Louis; or* A Textbook of Dental Pharmacology, Materia Medica and Pharmaco-Therapeutics (*$5*) *by McGehee and Green; Blakiston Co., Philadelphia.*—THE EDITOR

STRAIGHT FROM HEADQUARTERS

by ROBERT P. FISCHELIS, Secretary
AMERICAN PHARMACEUTICAL ASSOCIATION

EVER since public attention has been focused on the inability of certain groups within the population of the United States to obtain all of the benefits of modern medical care at a cost to them which they can readily afford, various proposals have been made to remedy the situation.

Perhaps the most far reaching of the early researches in this field was the five-year program of the Committee on the Costs of Medical Care. Its final report published in 1932, together with the many thorough-going studies which furnished the basis for the conclusions of the Committee, impressed the nation with the social and economic aspects of the medical care problem and stimulated widespread interest in finding a solution.

Every student of the subject has followed with interest the conflicting claims of producers and consumers of medical care and it was to be expected that debate on the subject would lead to a variety of charges and countercharges, as well as constructive proposals for meeting the situation.

The war developed new aspects of the problems of medical care and emphasized in various ways many existing deficiencies in the health of men and women which could be corrected by adequate and readily available preventive and curative measures. War medicine for both the armed forces and civilians brought into bold relief the possibilities of mass care and preventive measures and emphasized the extent to which pooling of our knowledge, skill, information and resources can improve health and make available the safeguards against sickness.

The American Medical Association has been gathering data for many years on the basis of which a sound program of prepayment for medical care could be evolved. Welfare organizations and individuals deeply interested in social progress have suggested procedures which have been termed socialistic by the more conservative segments of our population and by a majority of the organized medical profession. On the one hand, legislative proposals have been fostered, such as the Wagner-Murray-Dingell Bill which is typical of the method of solution recommended by some public health officials and welfare workers.

On the other hand, the medical profession, through its state and national associations, has been sparring for time by interposing objections at every stage of any process designed to place payment for medical care on anything approaching a compulsory insurance basis. In recent years the profession has been repeatedly reminded of the necessity of meeting the public outcry against alleged too high costs of medical care with a positive program, and such a program has been in the making for a number of years.

The success that has attended the Blue Cross prepayment plans for hospitalization has definitely stimulated the demand for complete sickness insurance. Many of these plans have already added laboratory service, X-ray and other diagnostic tests, and in some instances payment for surgical operations and special treatment.

It is plain, of course, that the physician is the central figure in any plan of medical care. Therefore, all plans to provide for more complete utilization of medical facilities for more people stress the importance of securing the approval and agreement of the medical profession to participate on a basis which appeals to the profession. From time to time there have been announcements, both from the profession and from lay groups, with respect to principles that should be followed in providing adequate and maximum health care.

The American Medical Association has finally issued its own national health program which relies on the nation-wide organization of locally administered prepayment medical plans sponsored by medical societies.

The Council on Medical Service of the American Medical Association has established a standard of acceptance for medical care plans and has laid down several provisos under which such plans may qualify for acceptance and carry the seal of approval of the Association. These provisos include (1) approval by a state or county medical society in the area in which the plan operates; (2) assumption by the medical profession of responsibility for the medical services included in

the benefits; (3) free choice of a qualified doctor of medicine and maintenance of the personal confidential relationship between patient and physician; (4) organization and operation of the plan to provide the greatest possible benefits in medical care to the subscriber.

To further these plans, an independent association known as "Associated Medical Care Plans, Inc.," has been organized and will include as members all plans that meet the minimum standards of the Council on Medical Service of the American Medical Association. Through this organization it is expected to provide coordination and reciprocity among the various plans to permit transference of subscribers from one plan to another and use of the benefits in any state.

The American Medical Association has also established a Division of Prepayment Medical Care Plans within its own organization with a director and staff who will administer the activities related to the promotion and development of medical care plans in all states.

A. M. A. Ten Point Plan

At a recent meeting of the House of Delegates of the American Medical Association, a statement of ten principles to solve the national health problem was adopted. These ten principles may be summarized as follows:

1. There should be individual responsibility for a minimum standard of nutrition, housing, clothing and recreation as fundamental to good health, but the application of community effort compatible with free enterprise should be encouraged, with governmental aid where needed.

2. The provision of preventive medical services through health departments is recognized as essential, but there should be local control over funds received from the Federal government for that purpose. Care of the sick as a function of health departments is, however, disapproved.

3. Maternal and prenatal care should be made available to all at a price they can afford to pay and when local funds are lacking for the care of those unable to pay, federal aid should be supplied but administered through local or state agencies.

4. Child health care should be supplied by the individual physician but may be provided through child care and infant welfare stations, administered under local auspices with support by tax funds whenever the need can be shown.

5. Health and diagnostic centers and hospitals are recognized as essentials of good medical care and the provisions of the Hill-Burton bill for such facilities with Federal aid are approved.

6. Private hospitalization insurance such as the Blue Cross plans and voluntary nonprofit prepayment plans for medical care are approved.

7. Veterans' medical care, preferably by a physician of the veterans' choice, with payment by the Veterans' Administration is endorsed on a basis of mutual agreement between state medical associations and the Veterans' Administration.

8. Research for the advancement of medical science with inclusion of medical research in a national science foundation sponsored by the Federal government is endorsed.

9. The services rendered by volunteer philanthropic health agencies and their participation in a national health program is encouraged.

10. Health education is recognized as fundamental to the promotion of the public health and alleviation of illness and is considered a necessary function of all departments of public health, medical associations and school authorities.

Thus, under the stress of the times and the revolution in national and international attitudes toward health and medical care as inherent rights of the individual, organized American medicine takes on new responsibilities. It agrees that complete medical care is not alone for the wealthy and the indigent, but also for the medically indigent and the low income groups whose means do not extend to the ability to meet the financial obligations of catastrophic illnesses without some organized form of preparation.

The familiar family doctor, easy-going as far as collections for his services are concerned, takes on a more businesslike attitude through his county, state and national associations, for they have agreed that making it possible for each patient to pay is better than charging the rich to compensate for services to the poor.

It is clear from popular discussions of the subject and the various opinion polls that the people of the United States believe the insurance principle applied to the more expensive medical services offers a sounder approach to a national health program than to saddle the medical profession alone with both the problem of providing good medical service and collecting the bill.

Other professions engaged in supplying medical services and supplies have been sympathetic with the views of organized medicine on this problem and are of course vitally interested in the program that is now evolving. Pharmacy is vitally interested in the trends and while it is not at the point of initiating any program of medical care it will always support the central figure—the doctor of medicine—in his efforts to maintain all medical services on a high, independent and altruistic level.

ACETARSONE

CARBARSONE

IODOCHLOROHYDROXYQUINOLINE

SECOND IN A SERIES ON DRUGS NEWLY ADMITTED TO N. F. VIII

by MELVIN W. GREEN

AMEBIASIS—invasion by the organism *Endameba histolytica*—occurs far more frequently than previously appreciated. Formerly there was a tendency to recognize only the most severe, acute attacks. These are accompanied by dysentery and are spoken of as amebic dysentery. Failure to recognize the more subtle forms of the disease brought failure to visualize its widespread character.

Craig,[1] in 1932, pointed out that 5 to 10% of the people in the United States at least harbor the disease. A complement-binding substance actually develops in the blood of these carriers, indicating some degree of tissue injury. The carriers constitute a genuine public health menace, especially among food handlers, as so well shown during the outbreak at the Chicago fair.

Historically, emetine has been considered for some time as the leading specific for amebiasis. Although emetine rapidly controls the symptoms of severe intestinal amebiasis, it is now thought to be the least active drug for actually curing the disease. Brown[2] claims that it is only about 50% effective and that there are many very undesirable side-effects leading particularly to peripheral neuritis and cardiovascular disturbances.

The moderate and limited usefulness of this drug led to the introduction of other drugs, notably acetarsone, carbarsone, and iodochlorohydroxyquinoline (Vioform).

Acetarsone

Acetarsone was introduced into medicine as stovarsol by Marchoux[3] in 1924. Being an arsenical it was also used in the treatment of syphilis. While moderately effective for this purpose and available physiologically upon oral administration, toxicity limits its usefulness as an antisyphilitic. As an amebicide it is effective in ambulatory cases and carriers.

The limitations of acetarsone are essentially those of carbarsone, but its toxicity is somewhat greater. It is generally believed that acetarsone has a therapeutic index about one-eighth that of carbarsone and it also exhibits more side-effects.[2, 4] Nevertheless, Brown[2] believes acetarsone to be an ideal complement to emetine—the emetine to control the acute symptoms and the acetarsone to destroy the amebae. No tragedies were observed in 232 cases, but toxic erythema was found in 5.6% of the cases along with an occasional exfoliative dermatitis. It appears that no arsenical should be administered unless the patient is under close observation.

The following table from Brown[2] is of interest:

Drug	Cure		Failure	
	Cases	%	Cases	%
Emetine	88	55	73	45
Ipecac	11	73	4	27
Arsphenamine	10	91	1	9
Acetarsone	112	85	19	15
Chiniofon	22	82	5	18

Acetarsone has been used also (as a powder containing 12.5% acetarsone in a mixture of equal parts of sodium bicarbonate and kaolin) in the local treatment of vaginal infections from *Trichomonas vaginalis*. In addition it has been used as a paste locally for Vincent's angina.

Standards for acetarsone and acetarsone tablets will be included in N. F. VIII.

Carbarsone

Carbarsone, first prepared by Ehrlich, was introduced as an amebicide by Anderson and Reed[5] in 1931. It is effective on motile forms of the organisms but is not so rapidly active as emetine. It does not act on amebae in liver ab-

Adapted from the *Bulletin of the National Formulary Committee.*

scesses, but is active against cysts. Because carbarsone is rapidly absorbed upon oral administration and rather slowly eliminated by the kidneys, rest periods between courses are needed to prevent cumulative toxic effects.

Deaths from carbarsone are extremely rare according to Epstein,[6] but mild skin rashes and localized edemas have been reported. Abdominal pains, diarrhea and vomiting may occur.

Most of the principles applying to acetarsone therapy apply also to carbarsone. The usual dose of carbarsone is 0.25 Gm. taken orally twice daily for about ten days, constituting a "course." After rest periods of ten days, this may be repeated several times if necessary. For acute dysentery, the drug is often given by rectum as a retention enema. In this case, after a cleansing enema, 200 cc. of a warm 1% solution of carbarsone in 2% sodium bicarbonate solution is repeated on alternate nights for 5 enemas.

Carbarsone is recognized by the U. S. P., and the tablets have been admitted to N. F. VIII.

Iodochlorohydroxyquinoline

Iodochlorohydroxyquinoline has been available for many years as Vioform and used as an antiseptic dusting powder in a manner similar to iodoform. It was found to be amebicidal by Anderson and Koch[7] in 1931. Later, Leake[8] found that the compound is rapidly excreted in the urine by humans and is very satisfactory against *E. histolytica* when given in capsules to monkeys. In 1933, David, Johnstone, Reed and Leake[9] made a more detailed clinical analysis of the compound and compared it with chiniofon, which is chemically similar in structure. The following table was prepared by these authors.

BIOL. ACTIVITY	IODOCHLOROHYDROXYQUINOLINE	CHINIOFON
Acute toxicity, oral, guinea pigs	200 mg./Kg. kills 13/20 in 4 days	900 mg./Kg. kills 7/15 in 6 days
In vitro amebicidal activity in 24 hrs.	Sol. HCl compd. 1:10,000	1:500
Balanticidal action in naturally infected guinea pigs	Cured 80% at divided dose of 150 mg./Kg. with 20% mortality	Cured 60% at divided dose of 600 mg./Kg. with 40% mortality
Amebicidal effect in naturally infected macaques	Cured 7/8 at 100 mg./Kg. for 10 days	Cured 2 at 500 mg./Kg. daily for 28 days; killed 2 at 2 Gm. daily for 10 days

These workers found no untoward effects in 57 unselected cases and 38 clinical cures were effected. After six months there were 6 recurrences out of 7 patients. A dose of 0.25 Gm., three times daily for a total of 15 Gm., was suggested with a repetition after a ten-day rest period. Ambulatory patients can use the drug without interference with their daily routine.

Because iodochlorohydroxyquinoline is not wetted by water, a wetting agent is incorporated into the commercial tablets.

The table on the next page modified from Beckman[4] summarizes these treatment plans.

One of the most important clinical uses of iodochlorohydroxyquinoline is the treatment of vaginitis, especially when due to infection by *Trichomonas vaginalis*. Allen[11] has pointed out that "at least in private practice *Trichomonas vaginalis* vaginitis is more common than gonorrhea." One of the most interesting clinical reports on the usefulness of iodochlorohydroxyquinoline in treating this form of vaginitis is that of Zener.[12] His criterion for cure was that of Adair and Hesseltine,[13] in which it is indicated that "the patient (without further treatment) has passed two menstrual periods without recurrence of symptoms, and there is no evidence of the disease on clinical appearance or smear."

While ointments containing this drug are effective, a high percentage of recurrences appear. Further, when ointments are used for a long time, a pad must be worn which increases the irritation. It is the opinion of Zener that the recurrences are often due to reinfection from the feces and, consequently, it is recommended that tablets be given orally in conjunction with any local treatment of the vagina.

In studying the *p*H range of the normal and diseased vagina, Zener found in the normal vagina a range of 4.6 to 7.5, with an average of 6.2. In the vaginitis patients he found a range of 4 to 5.6, with an average of 5. Since the more acute the vaginitis and the greater the number of organisms the lower the *p*H, Zener believes that local treatment should be alkaline. He recommended an insufflation of 1 part iodochlorohydroxyquinoline with 9 parts of magnesium trisilicate, using a total of 50 grs.

On the other hand, there are those who believe that a low *p*H inhibits the infecting organisms

SEVERAL ALTERNATIVE PLANS FOR THE TREATMENT OF AMEBIASIS WITH SPECIFIC DRUGS

FIRST COURSE OF TREATMENT	SECOND COURSE	THIRD COURSE
	(*To begin after ten days' rest*)	(*After ten days' rest*)
Emetine hydrochloride (subcutaneously or intramuscularly). A total dose not to exceed 10 mg. per Kg. Give two-thirds of the total amount in first six days; remaining one-third in second six days. (If not a case of moderate or considerable severity, the emetine may be omitted.)	Bismuth subcarbonate (or subnitrate), 12 Gm. in milk or water three to five times daily.	Bismuth salt may be continued as long as patient can take it.
At the same time give either one of the following:	At the same time either of the following depending upon which plan is being pursued:	
Plan A Carbarsone, 0.25 Gm. twice daily by mouth for ten days.	Iodochlorohydroxyquinoline, 0.5 Gm. twice daily by mouth for ten days. (Or chiniofon, 1 Gm. three times daily by mouth for eight days; or try the chiniofon enemas—see *Plan D*, 1st course.)	Repeat the carbarsone course by mouth or try the carbarsone enemas.
Plan B Iodochlorohydroxyquinoline, 0.5 Gm. twice daily by mouth for ten days. (Or chiniofon, 1 Gm. three times daily for eight days.)	Carbarsone, 0.25 Gm. twice daily by mouth for ten days. (Or carbarsone enemas—see *Plan C*, 1st course.)	Repeat either the iodochlorohydroxyquinoline course by mouth or chiniofon enemas.
Plan C Carbarsone, 200 cc. of 1% in 2% sodium bicarbonate solution by rectum, repeating on alternate evenings until at least five enemas have been retained overnight.	Iodochlorohydroxyquinoline, 0.5 Gm. twice daily by mouth for ten days. (Or chiniofon, 1 Gm. three times daily by mouth for eight days; or try the chiniofon enemas—see *Plan D*, 1st course.)	Repeat carbarsone enemas or try carbarsone by mouth.
Plan D Chiniofon, 300 cc. of 2.5% by rectum, to be retained as long as possible; repeated daily for ten days.	Carbarsone, 0.25 Gm. twice daily by mouth for ten days. (Or carbarsone enemas—see *Plan C*, 1st course.)	Repeat chiniofon enemas or try chiniofon or iodochlorohydroxyquinoline by mouth.

and promotes a more normal flora. As a reflection of this idea, commercial insufflates and inserts (vaginal tablets) are available containing boric and lactic acids as well as other ingredients.

Zener found that when insufflation was coupled with oral administration in 112 cases, the cures were 100% and there were no recurrences. When the drug was administered only vaginally in 28 patients, there were only 89% cures with 10.7% recurrences. Huffman[15] treated 14 cases with a 6% suspension of the drug in glycerin and got an excellent response. Peterson[14] treated 500 cases with a paste of 15 Gm. of iodochlorohydroxyquinoline in 22 cc. of glycerin and got nearly 100% cures and, in addition, found that 7 cases which were refractory to other forms of treatment responded well to iodochlorohydroxyquinoline.

Iodochlorohydroxyquinoline is recommended in petrolatum for the treatment of many forms of eczema and psoriasis.[16, 17]

Barkann,[18] in discussing the treatment of pyorrhea, suggests that in caring for infected alveolar pockets, the area should be packed with iodochlorohydroxyquinoline gauze after gentle curettement. The gauze is prepared by mixing the drug with one drop of glycerin to prepare a paste, which is then applied to gauze strips 1/4 inch by 1 1/2 inches. These packings may be left in place for as long as two days and then renewed if necessary.

Both iodochlorohydroxyquinoline and tablets of the drug will be official in N. F. VIII.

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JOURNAL PRESENTS

A. D. A. REPORTS ON DENTAL DRUGS

EVALUATIONS BY THE COUNCIL ON DENTAL THERAPEUTICS, TO APPEAR REGULARLY IN THIS JOURNAL, WILL INCREASE EFFECTIVE COOPERATION BETWEEN PHARMACY AND DENTISTRY

TO extend its service to readers, THIS JOURNAL has arranged with the Council on Dental Therapeutics of the American Dental Association to present regularly descriptions of products admitted to *Accepted Dental Remedies* and selected Council reports of interest to the pharmaceutical profession.

Since 1930, when the Council on Dental Therapeutics was organized, thousands of dental products have been considered, of which about 600 now stand accepted. Dental drugs, cosmetics, chemical mixtures and devices fall within the scope of the Council's investigations, which are carried out with the cooperation of the Bureau of Chemistry of the American Dental Association.

Although descriptions of accepted products may be based in part on evidence or information supplied by the manufacturer, such data are examined critically and are admitted only when supported by other evidence or when they conform to known facts. The Council and its employees make no charge to commercial firms for work in connection with the evaluation of products.

In the volume *Accepted Dental Remedies*, which is revised annually, pharmacists will find descriptions of all accepted products, together with their properties, actions, uses and dosage. Besides the formulas found in the body of the book, there is a formula and prescribing section designed for dentists "who wish to write prescriptions or to ask their druggist to prepare drug and chemical mixtures especially for them."

Dr. Donald A. Wallace, secretary of the Council on Dental Therapeutics, points out that "the Council encourages the writing of prescriptions, especially for sedatives and antiseptics. Dentists are also urged to develop a cooperative relationship with a local pharmacy, and to utilize the skill of pharmacists in the preparation of chemical mixtures for use in their work in the laboratory and at the chair."

Pharmacists who have added *Accepted Dental Remedies* to their reference shelf generally consider it both useful in their practice and helpful in developing more effective cooperation between pharmacy and dentistry. The volume is available at $1.50 from the Council on Dental Therapeutics, American Dental Association, 222 East Superior St., Chicago 11.

Products accepted between revisions of *Accepted Dental Remedies* are announced in the *Journal of the American Dental Association*, and now will be made available promptly to pharmacists through these pages.

Use of the Council's seal of acceptance, shown in the illustration, is permitted on those products which meet the standards for safety and effectiveness. The Council has formulated a set of ten rules to which products must conform in order to be eligible for acceptance. These rules cover ten pages of fine print,* but may be summarized briefly as follows:

Rule 1.—Products must be of known quantitative composition. The Council does not accept information in confidence.

Rule 2.—Scientific tests, adequate to standardize the product, must be known.

Rule 3.—Only certain classes of products may be advertised to the public, and these only in such a manner as not to encourage harmful self-treatment.

Rule 4.—Products must be labeled in such a manner as not to encourage harmful self-treatment. Accepted products must not be confused with unaccepted products in advertising or labeling.

Rules 5 and 6.—False or misleading claims for safety or effectiveness will not be permitted.

Rule 7.—Safety limitations of therapeutic,

* *Accepted Dental Remedies*, 11th Edition, pp. 7–17.

prophylactic or diagnostic devices must be stated plainly in printed matter accompanying the device.

Rules 8 and 9.—Names of products must be indicative of their composition where practicable. Exclusive proprietary names are not usually acceptable. Products with misleading names are not accepted.

Rule 10.—Products must be useful and compatible with the best interests of the public and of the dental profession.

The outstanding representatives of the dental profession and the basic sciences listed below are members of the Council on Dental Therapeutics. These men have no financial interest in any commercial enterprise and receive no salary or honoraria from the American Dental Association. The A. D. A. employs a full-time staff of six persons to carry out the details of the Council's program.

COUNCIL ↓ MEMBERS

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Harold S. Smith, D.D.S., Chairman of the Council, Chicago, Ill.

DENTAL REMEDIES

recently accepted by the
COUNCIL ON DENTAL THERAPEUTICS
AMERICAN DENTAL ASSOCIATION

ANESTHETICS—LOCAL[1]

Procaine HCl 2%, Epinephrine 1:25,000: Each cubic centimeter is stated to contain procaine hydrochloride, U.S.P., 0.02 Gm.; epinephrine, 0.00004 Gm.; sodium chloride, 0.0045 Gm.; sodium bisulfite, 0.0020 Gm., and distilled water.

Procaine HCl 2%, Epinephrine 1:50,000: Each cubic centimeter is stated to contain procaine hydrochloride, U. S. P., 0.02 Gm.; epinephrine, 0.00002 Gm.; sodium chloride, 0.0045 Gm.; sodium bisulfite, 0.0020 Gm., and distilled water. Marketed in cartridges, 1.8 cc. and 2.4 cc. Manufactured by the Graham Chemical Company, Jamaica, N. Y.

Procaine HCl 2%, Epinephrine 1:25,000.
Procaine HCl 2%, Epinephrine 1:50,000: Composition: See Graham Chemical Company. Distributed by the Ethical Dental Products Company, New York, N. Y.

Procaine HCl 2%, Epinephrine 1:25,000.
Procaine HCl 2%, Epinephrine 1:50,000: Composition: See Graham Chemical Company. Distributed by the Gold Dental Supply Company, Cincinnati, Ohio.

Procaine HCl 2%, Epinephrine 1:30,000: Each cubic centimeter is stated to contain procaine hydrochloride, U. S. P., 0.02 Gm.; epinephrine, 0.000033 Gm.; sodium chloride, 0.0045 Gm.; sodium bisulfite, 0.0020 Gm., and distilled water. Marketed in cartriges, 1.8 cc. and 2.4 cc.

Procaine HCl 2%, Epinephrine 1:50,000: Composition: See Graham Chemical Company. Distributed by the Guterman Dental Supply Company, New York, N. Y.

ZINC OXIDE-EUGENOL CEMENTS[2]

Zinc Oxide-Rosin-Eugenol Temporary Cement (Anodyne)-Caulk: Powder: Each one hundred grams is stated to contain zinc oxide, 69.65 Gm.; hydrogenated rosin,[3] 29.85 Gm.; zinc acetate, 0.5 Gm. Liquid: Each one hundred grams is

[1] *Accepted Dental Remedies*, Ed. 11, p. 39.
[2] *ibid.*, Ed. 11, p. 214.
[3] *ibid.*, Ed. 8, p. 191.
[4] *ibid.*, Ed. 11, p. 93.

stated to contain eugenol, 82.1 Gm.; corn oil, 17.9 Gm. Manufactured by the L. D. Caulk Company, Milford, Del.

DENTIFRICES[4]

Varady Tooth Paste: Composition: See Milk-I-Dent Dental Cream. Manufactured by Trade Labs., Inc. Distributed by Varady Cosmetics, Inc., Newark, N. J.

Watkins Tooth Paste: Composition: Each one hundred grams is stated to contain precipitated calcium carbonate (Sturge No. 50), 36.7 Gm.; glycerin, 22.8 Gm.; magnesium hydroxide, 7.5 Gm.; gum tragacanth, 0.56 Gm.; soap, 1.13 Gm.; water, 30.6 Gm.; saccharin, 8 mg., and flavors (oil of peppermint, oil of spearmint, methyl salicylate, geraniol, oil of cloves and oil of pimento), 0.7 Gm. Manufactured and distributed by the J. R. Watkins Company, Winona, Minn.

SURGEON GENERAL CONFERS WITH COMMITTEE

"WE will oppose to the utmost any effort made to abolish the Pharmacy Corps." Thus concluded the Committee on the Status of Pharmacists in Government Service following a conference with Maj. Gen. Norman T. Kirk, Surgeon General of the Army, held at the headquarters building of the AMERICAN PHARMACEUTICAL ASSOCIATION.

Those attending the special meeting called on February 15, shown in the photograph above, were: (seated l. to r.) Col. Francis P. Kintz, chief of personnel, Office of the Surgeon General; Dr. Robert P. Fischelis of Washington, D. C.; Maj. Gen. Norman T. Kirk, Surgeon General of the Army; Maj. Arthur H. Einbeck of West New York, N. J., Committee chairman; and Dean H. Evert Kendig of Philadelphia, former Committee chairman; (standing) Col. J. H. Michaelis of the General Staff; Dean Charles H. Rogers of Minneapolis; Dean Henry S. Johnson of New Haven, Conn.; Maj. Frank L. McCartney of Norwich, N. Y.; Dean A. G. DuMez of Baltimore; Dr. Robert L. Swain of New York; Dean D. B. R. Johnson of Norman, Okla.; Maj. Bernard Aabel, MAC, pharmacist and liaison officer from the Office of the Surgeon General to the AMERICAN PHARMACEUTICAL ASSOCIATION; and George H. Frates of Washington, D. C.

The Committee met to consider new developments in the chronically unsatisfactory Pharmacy Corps situation and to discuss with Gen. Kirk, and members of his staff and the Army's General

Staff, the present and future status of pharmacy in the Army.

Gen. Kirk stated quite frankly that the Pharmacy Corps had been unwanted in the Medical Department, since additional corps unnecessarily complicate administration of the Department. Because of the establishment of the Pharmacy Corps, other professional groups, such as optometrists, felt justified in demanding a separate corps, he pointed out. Instead of multiplying the present number of corps, Gen. Kirk expressed the conviction that the structure of the Medical Department should be further simplified for administrative purposes. To achieve this objective he recommended that a Medical Service Corps be established by act of Congress, which would absorb the Pharmacy Corps. This Corps would include, in addition to pharmacists, specialists in sanitary engineering, parasitology, optometry, clinical psychology, psychiatric social work and other fields.

Gen. Kirk explained that pharmacy would be set up as a separate section in this Medical Auxiliary Corps, with a pharmacy officer in immediate command. He maintained that the number of pharmacy officers and the development of their services would be as great as in a separately constituted Pharmacy Corps. Pharmaceutical service in this organizational setup would provide, he said, the same opportunities and advantages as a Pharmacy Corps.

Turning to objections which had been raised concerning the proposed commissioning of nonpharmacists in the Pharmacy Corps, Army representatives insisted that this procedure is permissible under Public Law 281-79th Congress. This measure authorizes increasing the commissioned personnel up to 25,000 officers in the Regular Army. In the absence of legislation covering postwar reorganization of the Army, P. L. 281 allegedly supersedes previous legislation, such as the Pharmacy Corps Act, during the period of recruitment of Regular Army officers from the wartime Army.

So far as the Medical Department is concerned, it was said that the only place where such officers—commissioned in the Sanitary Corps and Medical Administrative Corps—can be temporarily assigned is the Pharmacy Corps. Members of the Committee gained the impression that the effect of this move on the Pharmacy Corps was not considered important by the Army since postwar organizational plans of the Medical Department did not now include a place for the Pharmacy Corps as such.

After the meeting with Surgeon General Kirk and other Army representatives, the Committee reconvened to decide what course of action to take in the light of these developments. The Committee's stand was transmitted to the Surgeon General in a letter of March 8.

Although expressing appreciation to the Surgeon General for the opportunity afforded by his visit for a frank interchange of views, the Committee reaffirmed its stand on two major points.

In connection with the commissioning of nonpharmacists in the Pharmacy Corps as a temporary expedient, the Committee was "not convinced that this is the best procedure to follow." The members adhered to their contention that this policy is contrary to the provisions of the Pharmacy Corps Act. The Medical Administrative Corps of the Regular Army is still available for commissioning specialists who are not pharmacists, it was pointed out. Although use of the M. A. C. for this purpose is restricted by a limitation on rank to that of captain, the Committee expressed the belief that Congress would agree to amend the act, covering the M. A. C., to raise the rank available therein.

The Committee also expressed the "firm conviction that both your objectives and ours with respect to supplying an adequate pharmaceutical service to the Army can best be achieved by a separate corps, such as now exists under P. L. 130-78th Congress, provided such a corps was organized and established in conformity with the law and the intent of Congress. We appreciate the problems which confront you with the integration of the various types of auxiliary services required by the Medical Department of the Army and, of course, we have no objection whatever to the formation of a medical service corps in which these various specialists, exclusive of pharmacy, may be grouped."

The Committee expressed the belief that the practice of pharmacy constitutes a service which cannot be satisfactorily integrated with the various other groups of specialists.

"We assure you," pharmacy's representatives told Gen. Kirk, "that in continuing the Pharmacy Corps and in completing its organization you will have the full support of the entire profession, and if you will indicate how we can be of greater service to you in this connection, we shall be very glad to cooperate to the fullest extent. However, we will oppose to the utmost any effort made to abolish the Pharmacy Corps."

Organizations represented by the Committee on Status of Pharmacists in Government Service are the AMERICAN PHARMACEUTICAL ASSOCIATION, National Association of Retail Druggists, American Association of Colleges of Pharmacy and National Association of Boards of Pharmacy.

APOTHECARY SHOP NEARS COMPLETION

INSTALLING A. PH. A.'s "Old Apothecary Shop" in the U. S. National Museum, Washington, D. C., has been a meticulous and time-consuming task. Formerly known as the Squibb Ancient Pharmacy, this extensive historical collection was given to the AMERICAN PHARMACEUTICAL ASSOCIATION last year by E. R. Squibb and Sons. It includes fixtures and a complete stock of equipment and pharmaceutical relics representative of European pharmacy between the 15th and 19th centuries.

When the ASSOCIATION announced that the Shop would be placed on deposit in the National Museum, Dr. Charles Whitebread, pharmacist and curator of the Division of Medicine and Public Health, immediately initiated plans to make the exhibit one of the outstanding points of interest.

Since April, 1945, the work has gone steadily forward. After constructing an apothecary shop within the Museum, Dr. Whitebread called in a sculptor, artist and other craftsmen to finish the interior in authentic style.

In the photograph below, E. G. Cassedy, official illustrator for the Smithsonian Institution, is shown completing the ornate and colorful decorations of the ceiling. With careful attention to detail, Mr. Cassedy devoted six months to this phase of the work. Preliminary sketches were first put down on paper, based on authentic illustrations of 18th-century apothecary shops.

Another worker is shown above "antiquing" the painted plaster walls. A dark coat of paint is applied and then rubbed off while still wet to produce the effect of a time-worn interior.

Installation of the fixtures has just been completed, and it is expected that the Old Apothecary Shop will be opened to the public early in July. Surrounding the Shop will be other displays pertaining to the profession of pharmacy. ASSOCIATION and Museum officials believe that this section will be of keen interest to the some 2,000,000 persons who visit the U. S. National Museum annually.

STUDY OF SURFACE-ACTIVE AGENTS AS BASES

NON-AQUEOUS, WATER-MISCIBLE OINTMENT BASES APPEAR TO BE ADVANTAGEOUS; THREE OF NINE AGENTS TESTED DID NOT INHIBIT HEALING OR IRRITATE

STUDIES of 9 surface-active agents to determine their suitability as components of hydrophilic ointment bases have been reported in the *Scientific Edition* of THIS JOURNAL (35: 33, 1946). After testing for irritant properties, the investigators chose 3 substances—judged as nonirritating—for application to wounds in rabbits and found them to have little or no effect on the process of tissue repair.

The experiments were conducted by M. C. Dodd, F. W. Hartmann and W. C. Ward of the Eaton Laboratories' Research Department.

Surface-active agents offer possibilities as superior vehicles because of their ability to lower interfacial tension and to promote more thorough diffusion of medicament. Their excellent emulsifying properties provide ointments that are washable with water alone. This permits easy removal from injured tissue for frequent observation with a minimum of mechanical irritation.

These properties also make surface-active agents suitable as medicated cleansing agents for removal of debris and dirt, the authors point out. Moreover, the use of water in hydrophilic bases of this type is unnecessary.

Although washable bases of the oil-in-water type serve a useful and valuable purpose, some disadvantages have been noted: certain incompatibilities, weakening of the protective physical covering due to water, and the tendency of water to evaporate causing a deposit of oily constituent and a concentration of ingredients.

In view of this, experience with synthetic organic materials of the surface-active type suggested the possibility of compounding pharmaceutically acceptable bases which contain no water but have the recognized advantages of water miscibility.

Workers at the Eaton Laboratories selected 9 surface-active agents which, by their physical characteristics, seemed potentially useful for this purpose. Anionic, cationic and nonionic types are all represented in the following list:

1. Sulfonated hydrogenated castor oil (National Oil Products Co.), a water soluble material which has been reported as an ointment base [THIS JOURNAL, *Scien. Ed.*, 30: 145, 1941].

2. Carbowax 4000 (Carbide and Carbon Chemicals Corp.), a polyethylene glycol resembling paraffin in its waxy appearance.

3. Carbowax 1500, a mixture of polyethylene glycols having an appearance similar to white petrolatum. Several reports have appeared on the use of Carbowaxes in ointment bases [THIS JOURNAL, 4: 251, 1943; *Ann. Surg.*, 118: 741, 1943].

4. Trigamine Stearate (Glyco Products Co.) is a trade name for a product similar to triethanolamine stearate. For testing purposes it was necessary to compound this material as follows: Trigamine Stearate, 30%; propylene glycol, 70%.

5. Arlacel B (Atlas Powder Co.) is the trade name for mannitan mono-oleate. For testing purposes it was compounded as follows: Arlacel B, 85%; Carbowax 4000, 15%. Although Arlacel B is insoluble in water, it is considered a useful emulsifier which lends itself well to compounding non-water-containing bases.

6. Tween 60 (Atlas Powder Co.) is the trade name for a polyoxyalkylene derivative of sorbitan monostearate. It is somewhat analogous to Arlacel B, but is water soluble. For testing, this substance was compounded as follows: Tween 60, 90%; Carbowax 4000, 10%. Use of both the Spans and Tweens, supplied by this firm, in sulfonamide ointment bases has been reported to permit and enhance the release of medicament [*Surg. Gynecol. Obstet.*, 80: 85, 1945].

7. Glyceryl laurate (Glyco Products Co.) is the glycerin ester of lauric acid. This was tested undiluted.

8. Cationic Agent D (Victor Chemical Works) is essentially the stearyl amine salt of the stearyl amide of ethyl phosphoric acid.

9. Triton K-60 (Rohm and Haas Co.) is the trade name for cetyl dimethyl benzyl ammonium chloride.

Propylene glycol was used with the abovementioned 9 materials as an excipient in preparing bases.

Where possible, Dodd, Hartmann and Ward used the surface-active agents undiluted for determining irritant properties on laboratory animals and human beings and the effect on healing

of wounds in rabbits. In cases where this was impractical, the highest percentage level of the material that would permit a usable combination was employed.

The Carbowaxes were not tested since a thorough investigation by Smyth and co-workers had indicated the lack of irritation from these substances. Triton K-60 was not employed in the tests on rabbits because it was not available in the laboratory at the time.

The surface-active agents were applied to the eyes of rabbits and the intact skin of rabbits and humans to determine irritant properties. In the eye of a rabbit, sulfonated hydrogenated castor oil and Cationic Agent D were judged to be the most irritating. Trigamine Stearate and glyceryl laurate caused no more than hyperemia of the conjunctiva. Arlacel B and Tween 60 elicited no reaction. When applied to the depilated skin of rabbits sulfonated hydrogenated castor oil and Cationic Agent D again were found to be the most irritating of the substances tested, while Arlacel B had the least effect.

In tests on human skin, Arlacel B, Tween 60 and glyceryl laurate caused no irritation of the skin after forty-eight hours. Sulfonated hydrogenated castor oil, Trigamine Stearate, Cationic Agent D, and Triton K-60 behaved as primary chemical irritants, the authors reported.

On this basis the former 3 agents were selected as worthy of careful study in regard to their effect on the healing of experimental wounds. Six excisions from the depilated skin of each of 20 rabbits were made. Three excisions were used for testing the surface-active agents; the remaining 3 excisions on each animal were used as controls.

Observation of the wounds, recording of their size and renewal of treatment were carried out every other day until all wounds were healed. In commenting on the data from these tests, the investigators said:

"The wounds treated with glyceryl laurate (100%) healed at a rate similar to that of the control groups, with a negligible difference in size found at the end of the healing period. . . . It appears that glyceryl laurate had a very slight effect, if any, on the healing process.

"Wounds to which Tween 60 (90%) was applied also healed at almost the same rate as the controls. . . . Here, again, the effect of the material applied to the wound was slight.

"Considering wounds treated with Arlacel B (85%), the similarity of healing between the treated and control groups from start to finish is striking. . . . There was no adverse effect on healing by Arlacel B under experimental conditions."

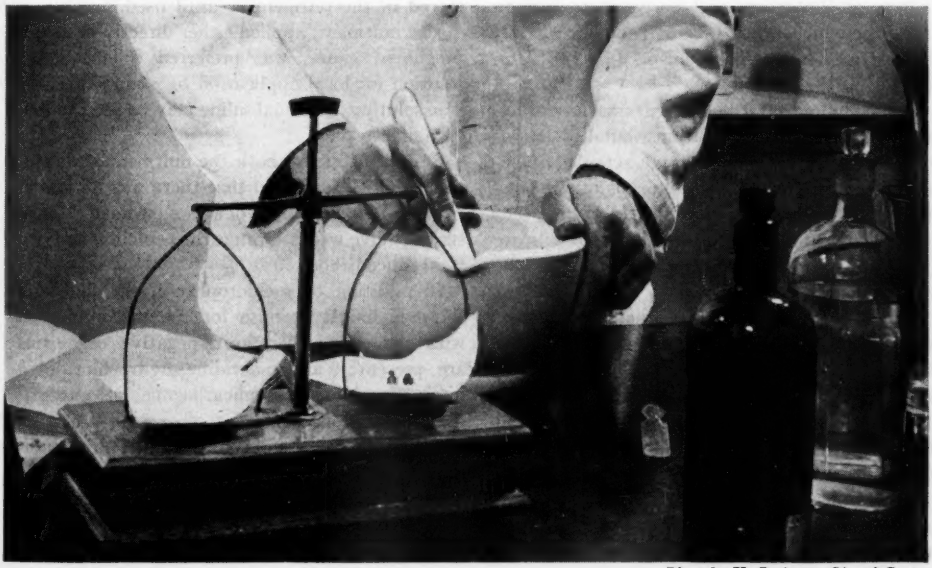

Photo by U. S. Army, Signal Corps

Microscopic findings from 6 biopsy specimens, taken from a representative rabbit, were "in good agreement with the gross observations."

Results of this work suggest "certain correlations between surface activity and cutaneous irritation which may be of value in the selection of such agents for use on the skin," it was concluded. "Data obtained as the result of irrita-

tion tests on human skin would seem to preclude alkalinity, per se, as the cause of cutaneous irritation from surface-active agents."

Instead, the authors point out, examination of the chemical structure of these substances in relation to experimental results "suggests an interesting observation on the correlation of ionic character with a high degree of surface activity and irritation. . . . The nonionic materials—the Carbowaxes, glyceryl laurate, Tween 60, and Arlacel B—were nonirritating.

"The results presented indicate that the ionic character of a surface-active agent is more important in the prediction of potential irritation than is its *p*H value. This would lead to the conclusion that nonionic surface-active agents are preferable for use as major components of ointment vehicles."

MIXED INFECTIONS TREATED WITH PENICILLIN

PARACHLOROPHENOL has been found to be a safe and powerful disinfectant for use with penicillin in treating mixed wound infections. It has been known for some time that the enzyme penicillinase, produced by many aerobic gram-negative organisms, inactivates penicillin. Over 200 compounds and antibiotics were tested by investigators at the Columbia University College of Physicians and Surgeons to find an antiseptic which would protect penicillin against the enzyme-producing organisms (*J. Am. Med. Assoc.*, 130:121, 1946).

One hundred thirty-four strains of gram-negative bacteria isolated from wound infections were tested for their destructive action on penicillin. To combat these organisms in the presence of penicillin, the investigators found that "of the antiseptics so far tested and which are available at present, parachlorophenol is the most effective."

Moreover, parachlorophenol had the properties which the investigators considered criteria for the antiseptic they were seeking: It had to be active in the presence of organic matter and able to penetrate pus or wound discharges and the surrounding infected tissues. It had to be soluble in water; it had to prevent growth of bacteria in a wound without retarding the healing of the wound and it had to be nontoxic in the amounts needed when used for local application to infected wounds.

Parachlorophenol is readily soluble in water or in isotonic solution of sodium chloride in a concentration of 1:200. For clinical application a 1:400 concentration was used in either (*a*) isotonic solution of sodium chloride or (*b*) Carbowax 4000-propylene glycol (45 to 55% by weight) ointment base.

The ointment is prepared by melting 45 parts of Carbowax 4000† together with 55 parts of propylene glycol, either over a free flame or in a hot water bath. When thoroughly mixed, sterilize in a dry oven at 140° C. for four hours and then allow to cool. When the mixture begins to solidify (40° C.), the penicillin, 1000 units per gram, and parachlorophenol*, 0.25%, are added. The ointment may then be incorporated sterilely into fine meshed gauze (piece by piece cut to a convenient size), placed in a container, and stored in the refrigerator until used.

The ointment, applied either directly or as impregnated gauze, was preferred to the saline solution for local application to wound surfaces. The solution in normal saline may be used to irrigate sinus tracts.

Stability tests on both the ointment and solution at 5° C. indicated that there was no loss of penicillin titer after two weeks' storage. After six to twelve weeks' storage the penicillin activity was reduced about 50%.

In addition to *p*-chlorophenol, the following showed clinical promise for use in conjunction with penicillin when gram-negative organisms are present: 9-amino-acridine hydrochloride, 5 nitro-2-furaldehyde semicarbazone, streptothricin and streptomycin.

The investigators recommend that the individual strain susceptibility of gram-negative organisms isolated from any given infection should be tested for the inhibitory action of the five agents, since the sensitivity of different strains within the same species as well as the sensitivity of different species varies greatly.

The investigators reporting on the treatment of mixed infections with penicillin were Frank L. Meleney, M.D., Balbina A. Johnson, B.A., and Frances Colonna, M.S., of New York, and Capt. Edwin J. Pulaski, MC, A. U. S.

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† A product of Carbide and Carbon Chemicals Corp., 30 E. 42nd St., New York 17.

* Available from Eastman Kodak Co., Rochester, N. Y.

A FURTHER NOTE ON MODERN PRESCRIBING TENDENCIES

by L. W. RISING, E. M. PLEIN, and J. STROM
UNIVERSITY OF WASHINGTON, COLLEGE OF PHARMACY

This is one in a series of analyses of prescription records by the authors, published in the JOURNAL *and elsewhere. See* THIS JOURNAL, *6: 47, 1945, for a preceding study and additional references.*—THE EDITOR

SUBURBAN pharmacies can have a fine volume of prescriptions, even in what appear to be unfavorable locations. We have recently completed a survey of such a pharmacy. During the four-month inspection period* it filled an average of 31 prescriptions each day.

The pharmacy is unpretentious and is situated next to a large railroad yard which takes away what would normally be considered a quarter of its trading area. But the owners are real pharmacists who work at their profession. Their over-all volume reflects this energy and enthusiasm and shows that the handicap of location can sometimes be overemphasized.

The data collected include the following:

1. Number of prescriptions filled:

New	779 or 27.56%
Refills	2,933 or 72.44%
Total	3,712

It is interesting to note how the shortage of physicians during the war has, in this instance, reversed the ratio of new to refilled prescriptions.

2. Number of ingredients per new prescription:

NUMBER OF PRESCRIPTIONS	
One ingredient	587
Two ingredients	103
Three ingredients	56
Four ingredients	23
Five ingredients	7
Six ingredients	2
Seven ingredients	1
Total	779

3. Prescriptions requiring compounding: 32.77%.

This is a more favorable picture than that shown in a number of recent surveys made by the authors and others in which the percentage of prescriptions requiring compounding was more nearly 20%.

4. Average selling price of new prescriptions: $1.25.

5. Number of drugs required to fill the 779 new prescriptions: 392.

6. Drugs used 10 or more times in filling the 779 new prescriptions:

Drugs	TIMES USED
Codeine phosphate, powder	58
Sulfathiazole tablets, 0.5 Gm.	37
Sulfadiazine tablets, 0.5 Gm.	30
Acetylsalicylic acid, powder	25
Empirin Compound with Codeine, 1/2 gr.	20
Nembutal Capsules, 1 1/2 gr.	16
Elixir phenobarbital	15
Syrup Cosanyl	15
Elixir terpin hydrate and codeine	14
Phenobarbital tablets, 1/4 gr.	13
Senodin Syrup	12
Sulfamerazine tablets	10

7. Combined tabulation of certain classes of drugs and of drugs and their preparations:

Codeine phosphate powder is the most popular single ingredient, being used 58 times in filling the 779 prescriptions. However, if all of the codeine salts, tablets and preparations, such as elixirs containing codeine, are combined, we find the drug used 148 times. Various other combinations among the 392 drugs when tabulated together provide interesting data on prescribing tendencies, as shown below:

Drugs	TIMES USED
Codeine, its salts, and preparations containing codeine	148
Sulfonamides and preparations containing sulfonamides	116
Barbiturates and preparations containing barbiturates	102
Vitamins	54
Acetylsalicylic acid and Empirin	54
Belladonna, atropine, and preparations containing these drugs	24
Hormones	23
Aminophyllin-containing preparations	10
Digitalis-containing preparations	7

* The survey covered the period November 1, 1944, to March 1, 1945.

PROGRESS IN ANTIMALARIA THERAPY

by JAMES A. SHANNON

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AND
DEPARTMENT OF MEDICINE, NEW YORK UNIVERSITY COLLEGE OF MEDICINE

AN AUTHORITY WHO PARTICIPATED IN THE SECRET WARTIME RESEARCH PROGRAM ON MALARIA OUTLINES FOR PHARMACISTS SOME OF THE RESULTS ACHIEVED . . . . PROPER USE OF ATABRINE EFFECTIVE CONTROL, WITH BETTER DRUGS ON THE WAY

STUDIES to improve antimalarial therapy have been carried on during the past four years in a rather comprehensive manner. The program of studies has been supported by the Committee on Medical Research of the Office of Scientific Research and Development, under the sponsorship of the National Research Council and the three Services. The various aspects of the program have been integrated during the past two years by the Board for the Coordination of Malarial Studies. This effort has involved the active participation of many synthetic chemists, biochemists and pharmacologists in academic and industrial laboratories, as well as clinicians in civilian and service installations.

It is the purpose of this brief presentation to give in outline the main course of these studies and to describe somewhat more fully some of the early experimental work with atabrine which permitted the effective management of the malaria hazard in the Services through the development of a proper usage of the drug.

The general program encompassed the study of the underlying disease mechanisms of the malarial infections, the biochemical characteristics of certain of the infectious agents, and the chemical characteristics of selected antimalarials. However, the major effort was devoted to a detailed study of such antimalarials as were already available and a search for more effective ones in a wide variety of chemical series.

The direction of the early work, i.e., in 1942–1943, was conditioned largely by the early loss to the United Nations of their normal sources of quinine and by reports, from the Services to the National Research Council and its committees, which carried the suggestion that atabrine as then used was of little use in the suppression and treatment of malaria.

These circumstances posed a problem to investigators in the summer and fall of 1942. There appeared to be no suitable antimalarial substance available in amounts sufficient to conduct large-scale military operations in hyperendemic malarious areas. Nor was there an adequate supply of antimalarial substance for the civilian populations of similar areas.

The solution of this problem came as the result of re-evaluating the potentialities of atabrine and the cinchona alkaloids other than quinine. From these studies it was clearly apparent that atabrine, when used properly, is a highly effective agent and one which is superior to quinine for the routine management of the malarias.[1,2,3] It was also apparent that any one of the cinchona alkaloids is roughly equivalent in effectiveness to quinine.[4]

The latter finding placed the use of a combination of the alkaloids, such as totaquine, on a reasonable basis. This permitted the use of cinchona barks of Central and South America (which are low in quinine) for the production of an effective antimalarial substance in large quantity and at relatively low cost. The product was then available to civilians at a time when quinine was withdrawn from the general market and when the production of atabrine was too small for any to be available for civilian use.

A second phase of the studies was concerned with the development of new antimalarials. It was believed that although an antimalarial is qualitatively similar to atabrine in the character of the antimalarial action it exerts, it might be superior if the tolerated dose is sufficiently in excess of that required to terminate a clinical attack. It was hoped that such an increase in antimalarial activity would not only be useful for suppressive purposes, but would also result in a

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* Presented as part of the Seventh Annual Scientific Award Ceremony of the American Pharmaceutical Manufacturer's Association, in honor of the Rockefeller Institute for Medical Research, December 10, 1945.

This paper is based partially upon work done under contracts recommended by the Committee on Medical Research between the Office of Scientific Research and Development and various universities. The work on atabrine reported in the latter part of the paper was as the result of such a contract between the Office of Scientific Research and Development and New York University.

curative action in vivax malaria through an effect upon the underlying tissue forms of the parasite. These forms are assumed to be responsible for relapses in this infection.

The search for compounds with such a wide spread between minimal effective and maximal tolerated doses has met with considerable success. Out of this effort have come several antimalarials which appear to be quite superior to atabrine. It is now possible to obtain complete suppression with the administration of a well-tolerated dose of an antimalarial at intervals of one week or more and an abrupt termination of a clinical attack in vivax malaria, and a cure of falciparum malaria when drug administration is limited to one or, at the most, two days.† These agents are still under active study but are now at the stage where the publication of the experimental basis for these statements, by the investigators directly concerned with the studies, is anticipated in the near future.

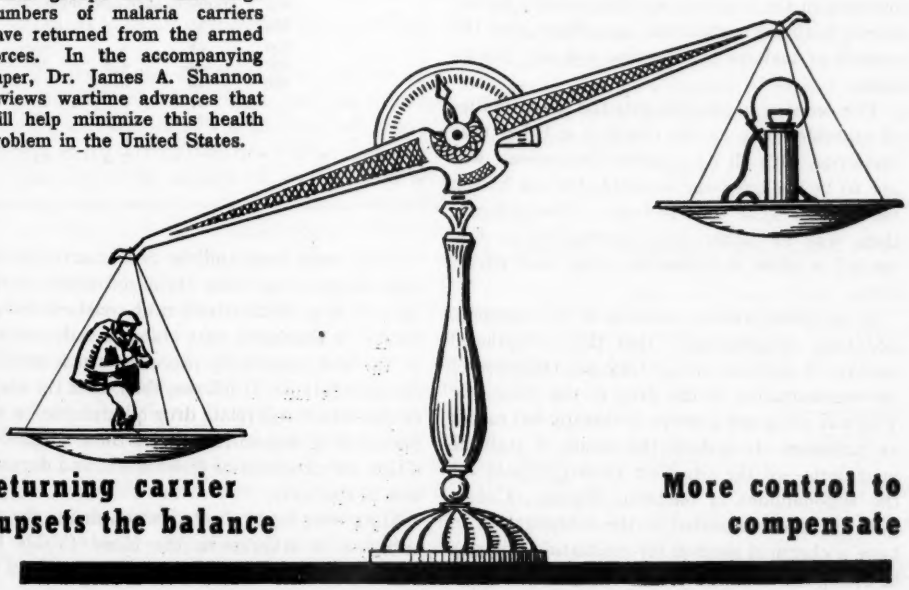
There is little doubt that these or other newer agents will supplant atabrine and contribute in no small measure to the successful control of malaria in many areas. However, other studies with these highly potent antimalarials indicate that such a simple, though reasonably extensive, increase in antimalarial activity as evidenced by the action of the drug in terminating a clinical attack, i.e., against the erythrocytic forms of the parasite, cannot per se be expected to lead to a curative action in vivax malaria.

The obtaining of this information marked the beginning of the third and present stage of the malaria studies. This is characterized by an approach to the problem of devising curative agents for vivax malaria. Such drugs are now assumed to require qualitatively different actions than those possessed by quinine and atabrine. It seems reasonably certain, as the result of investigations conducted during the past year,‡ that the older studies of the antimalarial activity of plasmochin led to conclusions which are essentially correct: that is, plasmochin administered at a high dosage has a prophylactic and curative action in vivax malaria, the curative effect particularly obtaining when the drug is administered concurrently with quinine for a long period of time, i.e., 14 to 21 days. As the result of these studies an extensive exploration of compounds analogous to plasmo-

† A statement concerning the potentialities of one of these compounds, SN-7618 (7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline), has recently been published in *Science*, **103**, 8 (1946).

‡ These studies were conducted by: (*a*) Dr. Alf S. Alving, Department of Medicine, University of Chicago; (b) Drs. Robert Coatney and W. Clark Cooper of the U. S. Public Health Service; (*c*) Dr. James A. Shannon, Department of Medicine, New York University College of Medicine; (*d*) Dr. Robert B. Watson, Tennessee Valley Authority and University of Tennessee, and their respective staffs.

BETTER CONTROL of malaria, through both preventive action against the vectors and proper use of effective therapy, must be encouraged by all public health groups now that large numbers of malaria carriers have returned from the armed forces. In the accompanying paper, Dr. James A. Shannon reviews wartime advances that will help minimize this health problem in the United States.



chin was undertaken. Investigations to date suggest that the prospect of obtaining a generally useful curative agent from this group of substances is rather bright, though highly speculative.

Such a summary statement does not give a very clear picture of what has been accomplished in terms of bettering our understanding of the malarias themselves, our ability to approach the problem of devising and examining antimalarials in a more effective manner, and our ability to deal with the malarial hazard in a practical manner. A general appreciation of each of these accomplishments will only be possible as the work of the many contributing investigators appears in the medical literature.

Atabrine Was In Ill Repute

Some insight into the general philosophy of one aspect of the studies can be gleaned from an examination of some of the early work with atabrine. To say that atabrine was in low repute in the spring and summer of 1942 is, at best, an understatement. It was not believed possible, in the wholly susceptible individual, to produce with atabrine a prompt termination of the clinical attack, more particularly in falciparum malaria, much less a cure in either falciparum or vivax malaria. Furthermore, the drug was reported to be both rather toxic and ineffective when used as a suppressive. Of immediate importance to the ultimate control of the malarias as a tactical problem in the Services, was the growing feeling among both the medical and line officers that the control of malaria by atabrine was not practicable.

The decision to reinvestigate the potentialities of atabrine came as the result of a belief that this drug, with all its apparent limitations, was apt to be the only one available for use by the Services for some time to come. The problem, then, was to gather such information as was needed in order to utilize the drug most effectively.

As an initial working premise it was assumed, and later demonstrated, that the antimalarial activity of atabrine at any time is a reflection of the concentration of the drug in the plasma.[2,4] This was not a new concept of therapy but rather an extension—to include the action of atabrine in malaria—of the situation known to hold for the sulfonamides in bacterial disease. Consequently, it was essential in the investigation to have a chemical method for estimating atabrine in biological fluids which has adequate sensitivity, precision, and specificity. Such a method was developed by Dr. Brodie of our Service in the fall and winter of 1942[5] and was immediately applied to the problem.

The investigations were initiated with a twofold purpose in view. The first was to define the relationship between the oral or other methods of administering atabrine and the concentration it achieves in the plasma. The second was to define the relationship between plasma atabrine concentration and its antimalarial effect. These two aspects of the problem are best dissociated experimentally and can be most easily discussed separately.

Physiological disposition of atabrine: It must be appreciated that the plasma atabrine concentration obtained at any time on any regimen of therapy is determined by the dosage utilized together with the net result of the processes of absorption, distribution, degradation and excretion. Atabrine is almost completely absorbed in the gastrointestinal tract and renal excretion accounts for very little of the daily dose (Table I).

TABLE I.—THE ABSORPTION AND EXCRETION OF ATABRINE IN MAN

These data may be taken as typical of the results obtaining during and just after the administration of 100 mg. of atabrine dihydrochloride three times a day to a normal adult.[1]

Day of Observation	Daily Atabrine	Plasma Concentration	Renal Excretion	Fecal Excretion
	mg.	micrograms/L.	mgm./day	mgm./day
1	300	36	...	...
2	300	28	...	...
3	300	32	4.8	30
4	300	48	5.5	7
5	...	37	7.3	36
6	...	17	3.3	10
7	...	...	8.0	6
8	...	...	2.2	11

From these facts and the fact that its plasma concentration becomes stabilized after several days of drug administration at constant dosage, it may be concluded that atabrine is disposed of by the body mainly by processes which result in its degradation. It follows, then, that the major factors which will relate drug administration and plasma drug concentrations are those which condition the processes of distribution and degradation in the body.

Data were first collected which define the distribution of atabrine in the blood (Table II). It was found that the relative concentration of the

TABLE II.—THE DISTRIBUTION OF ATABRINE IN HUMAN BLOOD

These data may be taken as typical of the results obtaining during the administration of 100 mg. of atabrine dihydrochloride three times a day to a normal adult.[1]

	Atabrine Concentration (microgm./liter)
Plasma	89
Plasma water	8.9
Cerebrospinal fluid	5.4
Erythrocytes	117
Leucocytes	18,400
Whole blood	551
Plasma binding (per cent total)	90

drug in plasma, erythrocytes and leucocytes is in the order of 1, to 1, to 100. This excessive localization of atabrine in the leucocytes acquired special importance in studies to assay the antimalarial activity of the drug, or to delineate the factors concerned with its physiological disposition. This is true because the concentration of atabrine in whole blood at any time during a period of therapy is more dependent upon the leucocyte count than the underlying chemotherapeutically active concentration in the plasma. It may be noted in passing that the major portion of atabrine in the plasma is bound to the nondiffusible constituents in the plasma. It would, perhaps, have been more precise were the studies of the physiological disposition and therapeutic activity of atabrine related to the concentration of unbound drug in plasma water. However, this appeared to be an unnecessary refinement at the time.

Studies on the distribution of atabrine in experimental animals indicated that the drug may achieve concentrations in the liver and spleen as high as 10,000 to 20,000 times those concurrently observed in the plasma. Localization in other tissues was found to be less extensive, but highly significant (Table III). An extension of these distribution studies to the human through indirect experimental approaches led to conclusions which were essentially similar. Thus, it was demonstrated that a major portion of the administered atabrine is localized in the tissues of the body, leaving little in the plasma to exert a chemotherapeutic effect. It is in consequence of this that unless large initial doses of the drug are given, the initial plasma drug concentrations are invariably low. However, the extensive localization, together with the low rates of degradation and renal excretion, lead to a low rate of decline of the plasma atabrine concentration. Consequently there is a low rate of loss of the protection conferred by atabrine, subsequent to the termination of drug administration.

Antimalarial Activity

The response of well-standardized and rigidly controlled blood-induced vivax and falciparum malaria to various plasma concentrations of atabrine was utilized to determine the antimalarial activity of the drug in terms of its ability to terminate or suppress a clinical attack.

It was found, in such infections, that the erythrocytic forms of P. vivax (McCoy strain) are completely and permanently eradicated when plasma atabrine concentrations of 30 micrograms per liter or more are maintained for not less than four days.

Plasma atabrine levels between 10 and 30 micrograms per liter generally produce temporary or partial effects. Levels below 10 micrograms per liter produce little or no effect when only maintained for a similar four-day period. The erythrocytic forms of P. falciparum (McClendon strain) appear to be more resistant and require approximately 50 micrograms per liter maintained for a six-day period for eradication.[4]

Subsequent work showed that the erythrocytic phase of a mosquito-induced vivax malaria (McCoy strain) has the same sensitivity to the chemotherapeutic activity of quinine as the blood-induced infections detailed above. The figures just quoted, then, have significance when applied to the naturally-acquired malarias. Subsequent work has also substantiated a previous belief that there are strain differences in susceptibility to the antimalarial activity of quinine, and these differences may be expected to extend in certain instances to the antimalarial activity of atabrine and other agents. However, the differences ob-

TABLE III.—DISTRIBUTION OF ATABRINE IN THE TISSUES OF A DOG

The dog received a daily dose of 20 mg. per kilogram of atabrine dihydrochloride daily for a period of 14 days prior to the experiment. The last dose was given 14 hours before the animal was sacrificed (wt. 10.0 kg.).[1]

	Atabrine Concentration (mg./kg.)
Plasma	0.061
Muscle	55.0
Lung	310.0
Spleen	571.0
Liver	1306.0

served have not been sufficiently great for one to expect that the regimens of atabrine therapy now in general use will be inadequate except in special instances.[4]

The correlation between oral dosage and antimalarial effect is poor so that it is difficult to state the activity of atabrine in terms of oral dosage. However, knowing the minimal plasma drug levels which are required to produce a given therapeutic effect and the range of plasma drug concentrations which are to be expected on a given dosage regimen in a group of individuals, it is possible to place the oral dosage sufficiently high for the maximal benefit to be derived from the drug for all but the exceptional individual.

Treatment of Clinical Attack

It was with an understanding of these aspects of the physiological disposition and antimalarial activity of atabrine that it was possible to consider rational regimens of therapy for both the suppression of the malarias and for the treatment of the clinical attack.

The primary objective to be sought in the treatment of the clinical attack is an abrupt termination of the clinical manifestations of the infection. The lower curve in Fig. 1 represents the mean daily plasma atabrine concentration of a group of individuals who received 0.1 Gm. of atabrine three times daily, a dosage schedule commonly recommended prior to 1943. Very low plasma drug concentrations are achieved with such a regimen during the first two or three days of therapy because of the extensive localization of the drug in tissues, as noted previously. It is true that the plasma level increases progressively throughout the period of drug administration as more and more atabrine accumulates in the tissue. Because of the early low levels, it is not to be expected that such a dosage will produce an early termination of clinical activity. If dosage is continued for a period of days, plasma drug concentrations are achieved which will terminate the clinical attack. However, it is the delay in the initial effect of atabrine, with such a dosage schedule, that led to the belief that atabrine therapy must be preceded by a two- to three-day course of quinine if an immediate effect is to be obtained.

The situation is quite different when doses of atabrine totaling 0.8 to 1.0 Gm. are administered during the initial day of therapy. This may be done by either the oral route or by a combination of intramuscular and oral administration. High plasma drug concentrations are obtained with oral regimens during the initial twenty-four

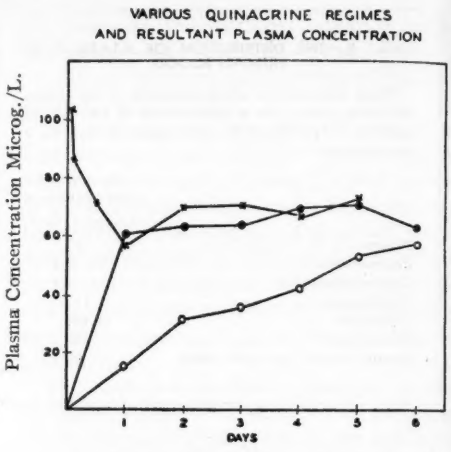


FIGURE 1

Data presented in previous publication.[3]

hours and with intramuscular regimens within fifteen minutes. These may be maintained with the serial administration of 0.1 Gm. three times daily for some six days thereafter. It was to be expected from such plasma drug curves that a therapeutic effect would be apparent very early during the course of drug administration and, in fact, such was found to be the case.

Suppressive Therapy

The various problems of suppressive antimalarial therapy were examined, using much the same experimental approach. As was to be expected from the excessive localization of atabrine in the body together with the low rates of degradation and excretion, it was found that the plasma atabrine level during suppressive therapy is dependent more upon the total weekly dosage than upon the pattern of the dosage regimen utilized. It was also found that when drug administration is limited to 0.4 Gm. weekly, as was initially advised, many individuals are found to have plasma drug levels which are considerably below those required to produce a demonstrable suppressive effect.

The data suggested that clinical malaria should be suppressed in all but a small proportion of individuals during active exposure to malaria by the weekly administration of 0.6 to 0.7 Gm. This

dosage in most individuals will result in plasma atabrine levels known to have a significant effect on the erythrocytic phase of the malarias. The unpleasant gastrointestinal reactions which were encountered when atabrine was administered in the earlier recommended dosage of 0.2 Gm. twice weekly are minimized and a therapeutic advantage gained when the larger total weekly dosage is administered in small daily doses of 0.1 Gm. Suppressive therapy of this type is commonly continued for a three-week period after the last exposure. This may be expected to accomplish cures of suppressed falciparum malaria but not of the suppressed vivax malaria. Clinical activity due to the latter will appear in most infected individuals within a few weeks to some months later, but may also be suppressed by a continuation of suppressive therapy. The latter procedure seems advisable when relapses are numerous and occur at short intervals.

Atabrine Best Available

Most of these facts were collected during the winter and spring of 1943 so that it was possible to recommend a change in the management of malaria in July of that year. These recommendations were accepted by the Services shortly thereafter, and, with minor changes, have been in use since that time.[6] The belief that atabrine, if used in a rational manner, would satisfy the immediate requirements of the Service for a practical and effective antimalarial was found to be justified. Comparing the results obtained with atabrine with those previously and concurrently observed with quinine, the Board for the Coordination of Malarial Studies concluded in the fall of 1944 that atabrine is quite superior to quinine for most purposes.[2]

The experience with atabrine very early in the malaria program was important for two reasons: First, as noted above, the rational use of the drug established it as one of extraordinary usefulness and one which satisfied an immediate and urgent need. Second, the observations with atabrine confirmed in a very dramatic manner the earlier belief that it is as important to define clearly the operation of those factors in the host which are concerned with the physiological disposition of antimalarial, as it is to define the antimalarial activity of the agent itself. This view has characterized the clinical study of antimalarials since that time and it is predictable that a similar view can be used with profit in the examination of therapeutic agents in diverse situations.

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ACTION OF ISONIPECAINE EXPLORED; SUGGESTS ANTIDOTE

Isonipecaine—the analgetic, spasmolytic and sedative—has been found also to possess considerable local anesthetic properties. Reporting on experiments in the *Scientific Edition* of THIS JOURNAL (35: 44, 1946), Dr. E. Leong Way of George Washington University School of Medicine estimates that isonipecaine is approximately seven-tenths as effective in this respect as cocaine.

The somewhat irritating properties of the drug preclude its use, however, as a local anesthetic. These findings nevertheless carry the implication, the investigator points out, that isonipecaine may have practical uses previously not realized. Preliminary experiments, for example, indicate that the drug, like certain other local anesthetics, may depress the irritability of the heart. Tests to determine its effectiveness against cardiac arrhythmias are therefore indicated.

Commenting on isonipecaine toxicity, Dr. Way suggests that "it would be logical to try to treat or prevent overdosage with agents similar to those used in cases of local anesthetic toxicity."

Tatum and others have indicated that the barbiturates are the preferable agents to employ. Not only are the barbiturates effective in arresting convulsions resulting from an overdose of local anesthetic, but if administered prophylactically the minimum fatal dose of the local anesthetic is increased three or four times.

Preliminary unpublished experiments by Dr. Way indicate that barbiturates act likewise when toxic doses of isonipecaine are administered.

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SUBSTITUTE FOR OLIVE OIL

Due to the unavailability of olive oil in this section, our leading dermatologist is anxious to find another vegetable oil to replace it in calamine liniment, N. F. Various oils have been tried without satisfactory results.—G. K., Ariz.

When olive oil is unavailable, it is possible and permissible to make preparations which require this ingredient by substituting cottonseed oil, U. S. P. This was authorized in the First Supplement to National Formulary VII.

Our laboratory has found this replacement to be satisfactory in the preparation of calamine liniment, about which you specifically inquired. However, on occasion cottonseed oil does not contain sufficient free acid to give a good emulsion with satisfactory stability. In such case we suggest that 0.5% oleic acid also be added.

ETHYLENE DISULPHONATE

I have inquired of several sources concerning ethylene disulfonate but have not received concrete information. Your advice, and the source of supply, will be appreciated.—E. W., Kentucky

Several pharmacists have inquired concerning ethylene disulfonate, marketed under the trade name Allergosil. This preparation has been the object of considerable investigation. While there have been favorable reports, it is claimed that the majority of investigators are not impressed with its possible therapeutic value.

The subject is now being reviewed by the Council on Pharmacy and Chemistry of the American Medical Association. A report will soon be published by this body, at which time further mention of ethylene disulfonate will be made in THIS JOURNAL.

When the product was launched as a cure for asthma the *Journal of the American Medical Association* considered it "another example of hasty and inadvised questionable promotional practice." In the January, 1944, issue of the *Journal of Allergy*, Collis and Hunt concluded from experiments that ethylene disulfonate "did not produce a significant degree of protection against anaphylactic shock."

B COMPLEX FOR INFANTS

Can you offer suggestions for vitamin B complex drops, nonalcoholic, for supplementary infant feeding?—W. G., Texas

The following formula from the *Bulletin of the American Society of Hospital Pharmacists* should fill your need:

	Gm./cc.
Thiamine chloride	1.25
Riboflavin	0.25
Pyridoxine hydrochloride	0.75
Calcium pantothenate	0.2
Nicotinic acid	5
Distilled water	200
Syrup cherry, *q. s. ad*	500

Dissolve the niacin and riboflavin in water with the aid of heat. Cool, add the other ingredients, and filter.

Dosage will be determined by the physician. The protective supplement prescribed in one hospital was 0.25 cc. or approximately 5 drops.

FORMULAS FOR MANUFACTURING

Please send list of books which deal with pharmaceutical formulas for manufacturing concerns.—M. H., Michigan

In addition to the U. S. P. and N. F., the following books should provide formulas of interest:

The Pharmaceutical Recipe Book (Third Edition)—American Pharmaceutical Association, 2215 Constitution Avenue, N. W., Washington 7, D. C., $5.

Pharmaceutical Formulas, Vols. I and II—Chemist and Druggist, 28 Essex Street, Strand, London, W. C. 2, England.

Chemical Formulary, Vols. I to VII—H. Bennett—Chemical Publishing Company, Inc., 234 King Street, Brooklyn, New York.

Drug and Cosmetic Review—Drug and Cosmetic Industry, 101 West 31st Street, New York, New York.

PLASTIC LINERS FOR DENTURES

I am interested in obtaining the formula of a plastic preparation for use by dentists in lining dentures which have become loose in the patient's mouth. It is a paste said to become an integral part of the denture after application.—M. M., New York

A number of so-called "permanent liners" are on the market. These usually consist of 35 to 60% methyl methacrylate resin in a volatile solvent or plasticizer, such as ethyl or amyl acetate or glyceryl triacetate. Several disadvantages of these preparations are revealed in studies by research associates of the American Dental Association (*J. Am. Dent. Assoc.*, 33: 304, 1946). They concluded that liners currently available tend to distort, weaken and soften the denture base resin. Much of this difficulty is due to the solvents used.

Evidence seems to indicate that liners produce temporary improvement in the fit of loose dentures, but results are not permanent nor comparable to an efficient rebase.

A survey of practicing dentists in regard to the use of liners revealed that 17 considered them temporary; 1, permanent; 8, entirely unsatisfactory. Half of the dentists claimed that the liners had no effect on occlusion, while the other half noted a disturbance. Sixty-three per cent observed no effect on the denture base, but the remainder noted such effects as warping, softening and decomposition.

SUNBURN PREVENTIVES

What may be used as a "sun screen" preparation? Could you also tell me what esculin is and where it may be obtained.—F. C., New York

A discussion of sunburn prevention appeared in the July, 1945, issue of THIS JOURNAL, together with the following formula which has been admitted to N. F. VIII as a sun-tan ointment:

	Gm.
Phenyl salicylate	5
Ethyl aminobenzoate	2
Titanium dioxide	1
Neocalamine	1
Yellow ferric oxide	0.1
Coumarin	0.1
White wax	2
Triethanolamine	0.5
Stearyl alcohol	8
Stearic acid	2
Glycerin	10
Distilled water, *q. s. ad*	100

Warm the triethanolamine and the stearic acid together on a water bath for 10 minutes, add the white wax and the stearyl alcohol, and continue to heat until completely melted. Dissolve the phenyl salicylate, ethyl aminobenzoate and the coumarin in this mixture. Add the titanium dioxide, neocalamine and yellow ferric oxide in a fine state of division, and mix well. Add the distilled water and the glycerin, which have been previously heated together to about 70°, with constant stirring. Continue the stirring until the emulsion formed has an ointment-like consistency.

N. F. Sun Cream has the advantage of being washable, but the fact that an application may be removed while swimming must also be borne in mind when it is used at the beach. This preparation is not completely effective in the sense of screening out all radiation, since tanning is usually desirable.

Esculin is a glycoside constituent of the bark of the horse chestnut and has been used to a limited extent, as a 4% solution or ointment, to protect

the skin from sunburn. All of the literature references at hand are in foreign publications. It is available in this country, however, from Glogau and Co., 1120 Rand-McNally Bldg., Chicago 5.

Another query, requesting a source of titanium oxide and red petroleum vet. jelly, no doubt stems from a study of sunscreens reported in the January 5, 1946, issue of the *Journal of the American Medical Association*. The object here, however, was to provide as complete protection as possible to marooned naval or aviation personnel. For example, red petroleum vet. jelly (Standard Oil Co.) was found to provide complete protection against strong sunlight for as long as twenty hours, a quality obviously undesirable to those desiring a suntan. Moreover, this impure petrolatum clings so tenaciously that it is very difficult to remove even with soap and water.

L. VAN ITALLIE OBSERVES 80TH BIRTHDAY

by GEORGE URDANG

DIRECTOR, AMERICAN INSTITUTE OF THE HISTORY OF PHARMACY

FAMOUS HONORARY MEMBER OF A. PH. A. SAVED FROM DEATH AT HANDS OF NAZIS BY U. S. ARMY

ON March 12 an honorary member of the AMERICAN PHARMACEUTICAL ASSOCIATION, Professor Emeritus Leopold Van Itallie of the University of Leyden, Holland, celebrated his eightieth birthday. This fact is all the more enjoyable as some time ago the sad news of the death of this venerable pharmaceutical scientist had been reported in the English pharmaceutical press. Another member of the Van Itallie family, lecturer at the University of Amsterdam, and his wife had committed suicide during the Nazi occupation of Holland, and apparently the two Van Itallies had been confused by the reporter.

It is little short of a miracle indeed that the old gentleman has survived all the tribulations which he had to go through. According to a communication just received from the secretary of the *Fédération Internationale Pharmaceutique*, Dr. T. Potjewijd, Leopold Van Itallie and his wife lived for years in different concentration camps and were finally transported to Theresienstadt, in most cases the last station before extinction in the gas chambers of Auschwitz or Belsen. The quick advance of the American armies saved his life and that of Mrs. Van Itallie as it saved about 35,000 others of the about 300,000 individuals who were brought to Theresienstadt from all the countries occupied by the Nazis.

A short sketch from the pen of Dr. Hugo H. Schaefer and a picture of Leopold Van Itallie appeared in THIS JOURNAL (12: 754, 1923) on the occasion of the election of the Dutch pharmaceutical scientist as an honorary member of the A. PH. A. This sketch gives a good account of the work done by L. Van Itallie and the honors conferred upon him until 1923. Thirteen years later, at the age of seventy, he retired from the professorship of pharmaceutical chemistry and toxicology at the University of Leyden. He had held the post for twenty-nine years, making this old university of Helmont, de le Boë Sylvius, and Boorhaave fame one of the European meccas of scientific pharmacy. Among the students who flocked to Leyden in order to have the advantage of Leopold Van Itallie's personal instruction was the American pharmacist, Elmer H. Wirth, now professor at the University of Illinois College of Pharmacy.

Throughout his life Leopold Van Itallie has been an ardent advocate of international cooperation. He was instrumental in the founding of the *Fédération Internationale Pharmaceutique*, for a time the president of this federation and for all the time of its existence one of its most efficient driving forces. The idea of an international pharmacopœia found in him its most energetic and influential promoter, and he set much hope in the League of Nations as a means to achieve his goal. The formation, by the Health Organization of the League of Nations, of the Technical Commission of Pharmacopœial Experts in 1937, undoubtedly goes back to the instigation and indefatigable endeavor of Leopold Van Itallie. It was likewise under the auspices of the League of Nations that he did his remarkable work on opium assaying.

It is but natural that so much successful ac-

tivity has been recognized and rewarded. The honorary membership in the A. PH. A. was only one of many similar honors accorded to him. The academic world, too, showed its recognition by conferring honorary degrees (Paris, Liége). We do not yet know whether the bronze plaque which was placed in the pharmaceutical laboratory of the University of Leyden in his honor has escaped the lust of destruction of the Nazis. But even if not, the memory of a man like L. Van Itallie does not need a monument of bronze or stone. It is perpetuated in his work.

—B—

PHILADELPHIA COLLEGE MARKS 125TH ANNIVERSARY

The Philadelphia College of Pharmacy and Science, oldest pharmacy college in America, celebrated the 125th anniversary of its founding at ceremonies held February 22. During the afternoon program, an honorary doctor of science degree was conferred on Dr. George Urdang, honorary member of the AMERICAN PHARMACEUTICAL ASSOCIATION and director of the American Institute of the History of Pharmacy. The honorary doctorate was also received by Paul A. Kind, College trustee and vice-president of the Kind and Knox Gelatin Co.

Speakers were Dr. Urdang and Dr. Roy K. Marshall, director of the Fels Planetarium. Addresses at the evening program were given by Dr. Edward L. Bortz of the University of Pennsylvania; Dr. George D. Beal, chairman of the A. PH. A. Council and assistant director of Mellon Institute; and Dr. Ivor Griffith, president of the College and member of A. PH. A.'s Council.

A. S. H. P. PUBLISHES PAPERS FOR HOSPITAL ADMINISTRATORS

To aid hospital administrators in making plans for improved pharmaceutical service, a series of papers on various phases of hospital pharmacy is being published in *Hospitals*, official journal of the American Hospital Association. The project has been arranged by the Program Committee of the American Society of Hospital Pharmacists, with Chairman Evlyn Gray Scott as coordinator.

Dr. Robert P. Fischelis, secretary of the AMERICAN PHARMACEUTICAL ASSOCIATION, contributed the initial paper entitled, "The Lengthened Shadow of the Hospital Pharmacist." Mrs. Scott has presented a discussion on the subject, "Administration of an Effective Pharmacy Requires a Sound Policy;" James P. Jones, of San Francisco discussed "The Hospital Formulary," and Albert P. Lauve, of New Orleans, "Standard Technical Equipment."

The papers tentatively scheduled for forthcoming issues are:

"Out Patient Department" by Donald A. Clarke, New York; "Economics of Hospital Pharmacy" by Paul F. Cole, Chicago; "The Number of Pharmacists in Relation to the Number of Hospital Beds" by Hans S. Hansen, Chicago; "Building or Remodeling the Hospital Pharmacy," for which an author has not yet been selected; "Pharmacy Committee" by Roger P. Marquand, Cleveland; "Parenteral Medication" by Leo and Ann Godley, New York; "Bulk Manufacturing" by Robert Kumpf, New Haven.

In regard to the objective of the series, Chairman Scott expresses the belief that "if the hospital administrator understands what should be demanded or expected from the hospital pharmacy, he will either stand back of the qualified pharmacist or help inaugurate conditions that will place hospital pharmacy service on the proper basis."

Reprints of the published papers will be supplied to the American Society of Hospital Pharmacists by the American Hospital Association.

PHARMACEUTICAL DIRECTORY

The revised and enlarged *Pharmaceutical Directory*, compiled from the records of the AMERICAN PHARMACEUTICAL ASSOCIATION, serves as a quick reference guide to official contacts and sources of information in every branch of the profession. Published on page 183 of this issue of the JOURNAL, the *Directory* will also be available in pamphlet form at ten cents to those who wish a separate copy for desk use. Send orders to the AMERICAN PHARMACEUTICAL ASSOCIATION, 2215 Constitution Ave., Washington 7, D. C.

VETERANS' ADVISORY GROUPS AUTHORIZED FOR STATES

Most state associations have now set up committees on veterans' affairs which will cooperate with field offices of the Veterans' Administration to provide guidance to men returning to civilian pharmaceutical practice or those who wish to complete their education in pharmacy.

In a message to state secretaries on behalf of the Joint Conference of A. PH. A. and N. A. R. D. executive groups, Dr. Robert P. Fischelis, A. PH. A. secretary, suggested that each committee on veterans affairs include representation from pharmacy colleges, the state pharmacy board, practicing pharmacists and the state association.

This plan was developed from a resolution of the last joint conference of A. PH. A. and N. A. R. D. which urged that advisory committees be established if acceptable to the Veterans' Administration. After conferring with Gen. Omar N. Bradley, director of the Veterans' Administration, A. PH. A. and N. A. R. D. formally presented a proposal to the Veterans' Administration in which it was pointed out that "there are several thousand pharmacy students and partially trained pharmacists who left college or various phases of the pharmaceutical industry in order to serve in the military forces. As these men return to civilian life they will, of course, require some guidance in establishing themselves either as employees of large units in the pharmaceutical industry or as owners and managers of independent pharmacies.

"Those men who require additional education or wish to pursue postgraduate studies or complete their undergraduate work in approved schools of pharmacy may need some assistance in selecting the proper courses and in spending their allowance for education wisely.

"Those men who wish to establish their own pharmacies," the communication explained, "should have guidance from more experienced individuals or organizations with respect to proper locations, the purchase of established pharmacies, and the expenditure of funds secured on loans for the purpose of entering upon the practice of pharmacy on their own account."

Recognizing that the regular facilities of the Veterans' Administration usually would not be prepared to advise on technical professional problems, Gen. Bradley replied that the "Administration fully appreciates the cooperative offer of these organizations and will be very glad to avail itself of the service suggested. . . ."

The state committees participating in the plan will have a relationship to the Veterans' Administration on much the same basis as that of wartime state advisory committees to the state director of Selective Service.

"We are greatly encouraged by the fine cooperation we are receiving from the Veterans' Administration," Dr. Fischelis commented, "and we now have an opportunity to place pharmacy on a high plane in this organization, as well as to help pharmacy veterans and ourselves in meeting the critical problems which confront all of us."

THIOURACIL PRESCRIPTIONS MUST CARRY WARNING

If thiouracil is placed in a prescription container it should be labeled with the warning which appears on the manufacturer's package, the Food and Drug Administration has announced.

Thiouracil carries the warning: "This drug may impair resistance to infection. The physician should be consulted at the first sign of sore throat, fever, or any illness during treatment with thiouracil."

"It is our opinion," said the FDA, "that obliteration, destruction, or removal of this warning from the labeling when the article is received in interstate commerce and dispensed pursuant to a prescription would constitute a violation of the Federal Food, Drug, and Cosmetic Act."

Section 503 of the Law, which provides exemption from certain labeling requirements for prescriptions, does not provide for any exemption concerning *adequate* warnings of this type, it is pointed out.

A. PH. A. ANNUAL MEETING

The American Pharmaceutical Association and related organizations will hold their annual meeting in Pittsburgh at the William Penn Hotel, August 25 through August 30, the A. Ph. A. Council has just announced. Further details will appear in the June issue.

Science News Capsules

BERIBERI, which kills tens of thousands each year in the Orient besides causing uncounted disabilities, could be eradicated at a cost of little more than ten cents per person per year. Rice, staple food of most Oriental people, loses much of its thiamin during milling and polishing. Answer to the beriberi problem, according to a report published by the National Research Council's food and nutrition board, would be to enrich white rice as our white flour has been enriched.

Age of the universe is now believed to be only slightly more than our earth. A quarter century ago astronomers estimated that the universe had existed for 5 trillion years, as compared with only 2 to 3 billion years for the earth. But modern research cuts the estimated age of the universe to only slightly more than the latter figure.

An all-electronic, general purpose computer, the first ever developed, has made its debut at the University of Pennsylvania. Capable of adding numbers in $^1/_{1000}$ second, it will help free scientists from time-consuming calculations. The first problem put on the machine, which would have required an estimated 100 man-years of trained computer's work, was completed in two weeks. Only two hours of this time was spent in electronic computing, the remaining time being devoted to checking and reviewing the results. The computer contains 18,000 electronic tubes.

Streptomycin is living up to its early promise of effectiveness against tularemia, a report of clinical trials at the University of Cincinnati College of Medicine indicates.

Insecticidal aerosol bombs, similar to those used by the Army, are expected to be in plentiful supply this summer. The formula used by the military is: 3% DDT, 2% of a 20% pyrethrum concentrate, 5% cyclohexanone, 5% lubricating oil, and 85% Freon gas as the vehicle. Prices are dropping sharply.

Rutin, a drug similar in chemical structure to vitamin P, has proved effective in reducing increased capillary fragility and may be commercially available yet this year.

Glareless glass, developed during the war for military optical instruments, is now being put to civilian uses. Chemical coatings are used for this purpose, a method far more useful than etching and other techniques previously tried. A 60% increase in light transmission by binoculars, and increased lens speed and fewer false images as applied to camera lenses have resulted from use of the treated glass.

Mycocidin, obtained from one of the Aspergillaceae, is the latest of the drugs found to be effective against tuberculosis bacteria in the test tube. As yet, none have shown striking promise clinically.

A two-ton glass working lathe, the world's largest, has been completed for use in producing super-voltage tubes for X-ray and betatron machines.

A record for broken marriages will probably be set this year. Fragmentary reports for 1945 indicate that the divorce rate last year had already increased sharply to hit a new high. Estimates for 1944 put the divorce rate that year two-fifths above the rate for 1938, according to the statistical bureau of the Metropolitan Life Insurance Co.

Niacin can be synthesized more cheaply by a process which starts with 5,7-dinitro-8-quinolinol, according to patent claims (No. 2,394,650) filed by Adolph Zimmerli, Highland Park (N. J.) chemist.

Mysterious element in the sun, never found on earth, is apparently also present in the new exploding star, T Coronae Borealis. As the modern theory of atomic structure leaves no place for such an unknown element, the "impossible" green line observed in the spectrum may be due to some known substance which shines in a peculiar way under special physical conditions prevalent in the sun's corona and in the nova.

More effective use of plastics will result from a long-range research program on fundamental engineering problems to be undertaken at M. I. T. The project is sponsored by the Plastics Materials Manufacturers Association.

Radioactive krypton, rare inert gas produced in the cyclotron, has been developed for the diagnosis and study of vascular diseases such as hardening of the arteries, trench foot and Burger's disease. Credit for this new technique goes to University of California scientists. Effects of certain drugs—such as adrenalin and histamine—on the circulatory system are also being studied by using the "tracer" method to follow the physiologic journeys of radio-

active krypton inhaled in conjunction with drug administration.

Match-box size radios utilize radio construction techniques developed for the proximity fuze. "Printed wire" reduces wiring of radio circuits to a two-dimensional lithographic process. A solution of finely divided silver is painted onto a ceramic plate by a roller which passes over a stencil of the wiring circuit. The hardened silver produces a silver wiring circuit instead of the usual copper wires. Resistors are painted in over another stencil with a solution of carbon. Condensers and midget tubes are then soldered to the circuit.

Neurosurgery is reported as the most effective method of arresting the pernicious, progressive type of hypertensive disease. Cures are not claimed but, used in cases where indicated, the operation promotes improvement and increased life span.

"Sleeping sickness" viruses from the Orient, Africa and South America may be transplanted to the U. S. due to the mass movements of men over the world, epidemiologists in the Hooper Foundation of the University of California warn. Their experiments show that at least one, the deadly Japanese "B" type, can be transmitted and propagated in the same manner as those now here. One such virus has recently migrated from South America to Trinidad.

Simmond's disease, a rare illness and rarely treated successfully, has yielded to testosterone in two cases treated at the University of California Medical School. The treatment recently restored general health and lost sexual function in a male youth whose pituitary gland had been destroyed in an accident.

Typhoid fever and diphtheria are ravaging most of Europe in a postwar epidemic wave that recalls the typhus fever epidemic in eastern Europe following the first World War. Only improved living conditions with restoration of safe water supplies are expected to check the typhoid which UNRRA reports 15 to 30 times more prevalent in central Europe than before the war.

Television broadcasting from relay stations carried aloft in blimps is proposed, with experimental equipment already in use. A similar plan calls for the use of planes flying in lazy circles high above the earth. Since television waves rarely reach beyond the horizon the airborne relay stations would greatly reduce the number of stations necessary if located on the ground. Long-distance transmission over coaxial cables is practical but expensive.

Television cameras will be put to an unusual use this summer at Bikini Atoll, where they will transmit to distant observers an on-the-spot view of experimental atomic bombing of ships. Another interesting sidelight of the experiments is the announcement that animals will be aboard the bombed ships to test biologic reactions to the explosion.

Motherless male insects have been produced at the University of Pennsylvania. Female insects were treated before mating with heavy ultraviolet irradiation. This destroyed or disabled the heredity-bearing chromosomes in their still-unfertilized eggs. When they were subsequently mated with males and the eggs thus fertilized, nothing but male chromosomes were available to form the essential parts of the new nuclei. So the new insects grew up with no trace of maternal heredity—their characters were all derived from the male parents. This is the first known instance of growth to full maturity of motherless individuals from irradiated eggs and the technique is expected to have scientific value in heredity studies.

Congenital malformations in children whose mothers had German measles early in pregnancy may not occur with unusual frequency as had been feared. A study of rubella cases recorded at the Milwaukee health department does not seem to bear out earlier reports of a correlation between the disease and malformations. Physicians have been urged to survey records elsewhere for more statistical evidence.

Side-show freaks who have "turned to stone" suffer from scleroderma, a disease which has been successfully treated in one case with dihydrotachysterol. The chemical is closely related to vitamin D and exerts a powerful effect on calcium utilization in the body. Cause of the disease remains unknown but calcium metabolism is disturbed, increasing the amount of calcium in the skin by about 30% in some patients.

Agranulocytosis has yielded to penicillin in a patient who developed the often-fatal disease while being treated with gold salts for chronic rheumatism. Similar results have been achieved in cases precipitated by use of thiouracil. These findings have important implications since agranulocytosis has been a serious complication of various types of therapy. Penicillin acts as a temporary substitute for the leukocytes, holding invading bacteria in check until the bone marrow can again replenish the supply of blood cells.

(Condensed from Science Service)

RETAIL PHARMACY ADVERTISING

A series of institutional newspaper advertisements for the retail pharmacist is being made available to one pharmacist in each community by Metro Associated Services, 275 Seventh Ave., New York 1. Meanwhile, in Chicago, the newly organized National Ad Service at 130 N. Wells St. has announced establishment of a similar service for the independent pharmacist on an exclusive franchise basis.

NNR

PRODUCTS RECENTLY ACCEPTED BY THE A. M. A. COUNCIL ON PHARMACY AND CHEMISTRY

Council descriptions of drug products are published regularly in This Journal as they are accepted. Rules upon which the Council bases its action appeared in the November, 1945 issue (6: 329, 1945) and may be secured in pamphlet form upon request to the Secretary, Council on Pharmacy and Chemistry, American Medical Association, 535 N. Dearborn St., Chicago 10.

CONTRACEPTIVE JELLIES AND CREAMS (See New and Nonofficial Remedies, 1945, p. 355).

The following article has now been accepted:

HOLLAND-RANTOS CO., INC., NEW YORK

U. S. trademark 213,756.

Koromex Jelly: A water-soluble jelly formed from tragacanth and gum acacia having a *p*H of 4.6, prepared from the formula:

	Per Cent
Boric acid	2.0
Oxyquinoline benzoate	0.02
Phenylmercuric acetate	0.02
Glycerin	10.0
Gum acacia	0.6
Tragacanth	2.5
Perfume	0.015
Butyl parahydroxybenzoate as preservative	0.02
Water	100

Actions and Uses.—See article Contraceptive Jellies and Creams.

Dosage.—5 cc.

SYRINGE APPLICATORS FOR CONTRACEPTIVE JELLIES AND CREAMS (See New and Nonofficial Remedies, 1945, p. 357).

The following article has been accepted:

HOLLAND-RANTOS CO., INC., NEW YORK

Koromex Vaginal Applicator: A transparent plastic tube threaded at the blunt, intravaginal end, to screw onto tubes of Koromex Jelly to permit filling by compression of the tube. The full capacity is 5 cc., the recommended dose.

ACETARSONE (See New and Nonofficial Remedies, 1945, p. 235).

The following dosage form has been accepted:

ALLEN LABORATORIES, INC., PALMER, MASS.

Allen Brand Tampon with Acetarsone (Stovarsol): A lightly compressed stitched tampon of absorbent cotton, coated with 0.1 Gm. of powdered acetarsone, to which is attached a tablet consisting of acetarsone 32 mg. in a tablet base composed of lactose, dextrose, boric acid and starch with a small quantity of sodium bicarbonate and tartaric acid to aid disintegration.

Actions and Uses.—(See article on Acetarsone.)

Dosage.—Intravaginally, one tampon tablet every other day or daily, followed by a mildly acid douche after a third treatment or after a week's treatment, has been reported to give satisfactory results.

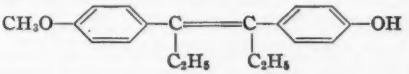
THIAMINE HYDROCHLORIDE (See New and Nonofficial Remedies, 1945, p. 610).

The following dosage form has been accepted:

FREDERICK STEARNS & CO., DETROIT

Tablets Thiamine Hydrochloride: 3 mg.

MONOMESTROL.—Mestilbol.—Diethylstilbestrol monomethyl ether.—3-*p*-Hydroxyphenyl-4-*p*-methoxyphenyl-3-hexene. — α,α'-Diethyl-4'-methoxy-4-stilbenol.—$C_{19}H_{22}O_2$ (Molecular weight 282.37). Monomestrol may be represented by the following structural formula:



It may be prepared by methylation of diethylstilbestrol or by partial demethylation of the dimethyl ether of diethylstilbestrol. The crude product may be purified by distillation in vacuum and recrystallization from water-alcohol or from benzene-petroleum ether mixtures.

Actions and Uses.—Monomestrol is used for the same conditions for which estrogenic substances are employed, and the contraindications are essentially the same. Like other estrogens, it must be individualized since each patient presents special problems. Patients undergoing treatment should remain under constant medical supervision. Side effects are rare, but when they do occur they are usually milk, although in a few instances it may be necessary to reduce the dosage temporarily.

Dosage.—The average oral dose for the treatment of menopausal symptoms is 0.5 to 1 mg. daily by mouth, although if necessary 10 to 25 mg. may be given parenterally biweekly. Dosage for atrophic genital disorders such as kraurosis vulvae include 1 to 5 mg. daily by mouth or 25 mg. weekly by parenteral injection; for gonorrheal vaginitis of children 0.25 mg. daily; for the prevention of breast engorgement 5 to 10 mg. daily or 25 mg. the first and third days by injection; for suppression of lactation 10 mg. two or three times daily, or 25 mg. daily by injection; for prostatic cancer 2.5 mg. three times daily by mouth. The duration of treatment varies and may last for several months or even two or three years in the treatment of the menopause, a few weeks for gonorrheal vaginitis in children, a few months for atrophic genital disorders, three to five days for prevention of breast engorgement and suppression of lactation or be continuous for prostatic cancer.

Tests and Standards.—

Monomestrol occurs as an odorless, white, crystalline powder, which melts at 116–117.5 C. when recrystallized from benzene-petroleum ether (112–114 C., when recrystallized from alcohol). It is soluble in alcohol, freely soluble in acetone and in ether and practically insoluble in water, in dilute

mineral acids and in dilute aqueous solutions of sodium and potassium hydroxide. It may be dissolved in vegetable oils and in dilute solutions of sodium or potassium hydroxide in 50 per cent ethanol.

To 1 mg. of monomestrol dissolved in 5 cc. of alcoholic potassium hydroxide add diluted hydrochloric acid to neutralize the solution and then add 1 cc. in excess. Add 1 cc. of molybdophosphotungstate reagent and shake. Allow to stand ten minutes, dilute to 25 cc. with water and add 5 cc. of saturated sodium carbonate solution: a blue color develops on standing. Add a few drops of 50 per cent solution of antimony pentachloride in dry *alcohol-free* chloroform to a dilute solution of monomestrol in the same solvent: a red colored solution is produced which changes rapidly to purple (*distinction from hexestrol, which gives no color*).

Dissolve 10 mg. of monomestrol in 5 cc. of concentrated sulfuric acid: an orange color is produced which disappears on dilution with water (*distinction from hexestrol and benzestrol, which give no color*).

Dry an accurately weighed specimen of monomestrol at 100 C. for four hours: the loss does not exceed 0.5 per cent. Ignite an accurately weighed specimen of monomestrol after the addition of concentrated sulfuric acid: the sulfated ash residue is not more than 1 per cent.

Transfer 0.1 Gm. of monomestrol to a 100 cc. volumetric flask and dilute to the mark with carbon tetrachloride. Transfer 10 cc. of the solution to a 250 cc. iodine flask fitted with an accurately ground stopper; add the calculated quantity plus 1 cc. of tenth-normal bromide-bromate solution (prepared according to the U. S. P. XII, p. 749); wash the walls of the flask and wet the stopper by the addition of 10 cc. of distilled water. Quickly add 10 cc. of 10 per cent hydrochloric acid and insert the wet stopper. Shake the mixture thoroughly for several minutes, then set aside in the dark at 30 C. and shake intermittently for exactly fifty minutes. At the end of this period place 2 cc. of 40 per cent potassium iodide solution around the stopper. Remove the stopper just enough to allow the potassium iodide solution to enter the flask, shake thoroughly, rinse the stopper and sides of the flask with distilled water, add 25 cc. of carbon tetrachloride and titrate with fiftieth-normal sodium thiosulfate to the disappearance of the pink color in the carbon tetrachloride. Each cubic centimeter of tenth-normal bromide-bromate solution is equivalent to 4.706 mg. of monomestrol. The monomestrol content is not less than 99 per cent. *The nature of the reaction between bromine and monomestrol leads to complications unless the conditions of a given procedure are strictly observed. This method of standardization must be considered tentative until more accurate analytic procedures are available.*

The following dosage forms have been accepted:

WALLACE & TIERNAN PRODUCTS, INC., BELLEVILLE, N. J.

Tablets Monomestrol: 0.25 mg., 0.5 mg., 1.0 mg., 2.5 mg. and 5.0 mg.

Solution Monomestrol 10 mg. and 25 mg. per cc. (in Sesame Oil): 1 cc. ampuls.

PROCAINE HYDROCHLORIDE (See New and non-official Remedies, 1945, p. 97).

The following dosage form has been accepted:

GEORGE A. BREON & CO., INC., KANSAS CITY, MO.

Solution Procaine Hydrochloride 2% W/V: 30 cc. vials. Each cubic centimeter contains 20 mg. procaine hydrochloride in isotonic solution of sodium chloride with chlorobutanol 0.5 per cent as a preservative.

PERTUSSIS VACCINE COMBINED WITH DIPHTHERIA TOXOID (See THE [A. M. A.] JOURNAL, Jan. 5, 1946, p. 31).

The following dosage form has been accepted:

PARKE, DAVIS & CO., DETROIT

Dipththeria Toxoid-Pertussis Vaccine Mixed (Sauer): 6 cc. vials (one immunization) and 24 cc. vials (four immunizations).

LAMBDA KAPPA SIGMA MEETS

Lambda Kappa Sigma, national pharmacy sorority, will hold its 1946 convention in Portland, Ore., June 22 to 26. This will be the first meeting of the organization's 26 chapters since 1940.

A. Ph. A. Branches

NORTHERN CALIFORNIA BRANCH—Rapid transportation to the hospital area; blood substitutes and sulfonamides; and a good hospital staff were described as the most important factors in caring for the wounded, by Dr. T. Eric Reynolds in an address before the Northern California branch. Dr. Reynolds, who served as a captain on Admiral Halsey's staff in the South Pacific, gave an interesting description of the difficulties encountered by his unit in landing on the islands to establish hospitals, and the trying conditions under which patients were treated. He praised the marvelous assistance given to the medical staff by the Pharmacists Mates who, in a majority of cases, were pharmacists. While in Japan, Dr. Reynolds had the opportunity to visit the pharmacy schools and found them to be excellent.

The meeting, arranged and conducted by the East Bay members, was exceptionally well attended. Louis Fischl and Eugene Sbarbaro were in charge of arrangements. Dr. T. C. Daniels, dean of the College of Pharmacy, University of California, gave a brief talk on the importance of the AMERICAN PHARMACEUTICAL ASSOCIATION.

CHICAGO—The local branch celebrated its 300th meeting on December 18th with a dinner at the Chicago Illini Union Building of the University of Illinois. A. PH. A. Secretary Robert P. Fischelis, guest of honor, addressed the members on the history, work and aims of the ASSOCIATION. The meeting was the first of three having representatives of societies of the health professions as speakers.

PHILADELPHIA—"Malaria" was discussed at the January meeting by the principal speaker, Dr. Justus B. Rice, vice-president in charge of research of the Winthrop Chemical Co. In reviewing the history of malaria, the speaker pointed out that the disease has helped destroy a number of civilizations and has affected the outcome of many wars. Dr. Rice proceeded to discuss the etiology of malaria and therapy, including new drugs developed during the war.

The branch secretary, John E. Kramer, read a bulletin announcing the temporary cancellation of Civil Service examinations for pharmacists due to adoption of higher standards, and a reply from the Army Surgeon General's office concerning the Pharmacy Corps.

NORTHERN CALIFORNIA—New officers for 1946 are Paul Marcucci, president; Charles

Shalz, vice-president; James Staven, secretary; and Eugene Sbarbaro, treasurer. Those elected to the Board of Directors were Dr. T. C. Daniels, Carl Tasker and Francis Spinelli.

At a recent meeting Dr. H. S. McCorkle of the University of California spoke on "Research and Clinical Use of Penicillin."

NORTHWESTERN—At a well-attended session, Dr. Frederick J. Wulling, dean emeritus of the University of Minnesota College of Pharmacy, delivered the third Melendy Memorial Lecture. He recounted many personal experiences with outstanding pharmaceutical figures of bygone years.

NORTHWESTERN OHIO—Dr. A. A. Brindley, Toledo physician, addressed the January local branch meeting on Federal health insurance. Opposing the Wagner-Murray bill now before Congress, Dr. Brindley urged members to take action to defeat the legislation.

Dr. George L. Baker, who aided in training pharmacist's mates during the war, described the Navy course and expressed the belief that many pharmacist's mates hope to become registered pharmacists without further training when discharged. Although recognizing the excellent work of the men at the battle fronts, Dr. Baker pointed out that they lack professional training for the practice of pharmacy and warned against lowering of professional standards.

NEW YORK—Dr. Charles H. Mann, chief of Squibb's Department of Professional Relations, spoke at the January meeting on "The Present Status of Penicillin, Streptomycin and Other Antibiotics."

In submitting the report of the Education and Legislation Committee, Samuel A. Dreyer reported that the proposed N. Y. City barbiturate regulations were not to be acted upon by authorities pending the enactment of state legislation.

NORTH PACIFIC—The following officers have been elected by the branch for 1946: Harvey Donnell, president; L. C. Britt, first vice-president; William Bush, second vice-president; and Fred A. Geue, secretary-treasurer. The branch has launched a program to raise funds for purchasing equipment for a modern manufacturing laboratory at the Oregon School of Pharmacy.

ST. JOHN'S COLLEGE—Dr. Louis J. Neff of the American Cancer Society addressed the student branch members at the January meeting. In discussing the problems of cancer control and treatment, he pointed out that the pharmacy is an outlet for helpful information to the community and may help promote control of the disease.

During the business session, A. PH. A. circulars on the Remington Medal award and the barbiturate conference were read. Miss Lydia Schick presented a paper on standards of the modern pharmacy, with reference to the discussion by J. W. Snowden in the December issue of the JOURNAL.

FROM THE SECRETARY'S FEBRUARY DIARY

—1st—

TODAY joined Dr. Powers in receiving U. S. P. Chairman E. F. Cook and Adley Nichols, U. S. P. trustees' secretary who came to discuss problems of mutual interest to N. F. and U. S. P., at Headquarters, and later at lunch at the Roger Smith. And there was no difficulty in achieving a meeting of the minds. Later a call by telephone from Jack Purinton, who now goes to G. D. Searles to manage production after successfully guarding the interests of the Surgeon General of the Army in the Drug Requirements Committee.

—2nd—

A Saturday morning conference with Justin Powers on many problems and then a bee-line for the train to Trenton, where routine business was disposed of before journeying to Red Bank for a short week-end.

—3rd—

A part of this Sunday given over to the special meeting of the Conference of Allied Medical Professions of N. J., which had been called to prepare argument against a bill pending in the legislature which would abolish the State Board of Health and substitute a Council without specific representation for the various professions; and the Conference considered this a step backward, filing a brief with the proper committees of the legislature, setting forth its views in no uncertain terms.

—4th—

An early morning start for Providence, R. I., to investigate facilities for the next convention which the ASSOCIATION decided two years ago should go to this New England city. All the afternoon with Miss Bennett, Biltmore Hotel convention manager; Dean Rivard; and Charles F. Gilson, looking over the meeting facilities of the hotel, and later to dinner, sampling the convention menus and entertainment provided in the Garden Restaurant and The Bacchante, and decided everything would probably pass muster, for there was entertainment of a kind to suit those who may come from the interior, as well as sophisticated New Yorkers.

—5th—

Off to an early start by rail to Boston, arriving within an hour and going straight to the Statler for more "convention shopping" and later to luncheon with Dean Newton and members of the Massachusetts College of Pharmacy faculty at the College building. After brief conferences with Dean New-

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ton, Professors Youngken, Kelly, Lynn and others, decided that if conditions in Providence failed to materialize to the satisfaction of the Council, Boston might fill the bill. But conversation with Copley Plaza and Statler Hotel officials brings out that they are long on service but short on available dates. Martin Adamo and Sam Silverman of the Massachusetts Pharmaceutical Association will step into the breach, if necessary.

—6th—

Up in time to leave Boston for Worcester on the B & A at 8 o'clock, with Adamo, Silverman and other Bostonians, bound for the mid-winter meeting of the Massachusetts Pharmaceutical Association. At Worcester, found many an early bird at the Sheraton Hotel ready to take part in the business of an important and well-attended meeting. Promptly at 10:30 a. m. Willard Chagnon sounded the gavel and routine business was promptly cleared to give us an early opportunity to address the assembled multitude on "Pharmacy in the Affairs of the Nation." It was particularly pleasing to endorse Gen. Omar Bradley and his capable Surgeon General, Paul R Hawley, who had been attacked in the newspapers by the national commander of the American Legion —quite unjustly, to our way of thinking. This became front-page news in the afternoon paper. Left Worcester on the 1:20 p. m. train for New York after exchanging greetings with many old and new friends including Anita DesRochers, New Hampshire Pharmaceutical Association treasurer; George Archambault, now heading the professional service activities of the Liggett Company; Frank East, William Briry, and many others. Reached New York late, but in time for the 7:30 to Washington.

—8th—

A welcome visitor was Capt. Arnold Singer, just in from India, where he had served capably for several years as bacteriologist in the Sanitary Corps with opportunity to experience infections on his own account; now ready to take on new responsibilities in New Jersey. An early afternoon conference with Army Surgeon-General Norman Kirk, Colonels Michaelis and Kintz, Major Aabel and Captain Wilson on the future of the Pharmacy Corps—a frank and free discussion.

Later with Major Aabel at our office discussing pharmacy's place in the Army, and finding much food for thought in his experiences as a member of the M. A. C. Like many another good pharmacist, this Minnesota graduate did not see service in the Pharmacy Corps.

—11th—

This morning a very worth-while conference with Assistant Dean R. B. Smith of the Medical College of Virginia School of Pharmacy, who heads the

A. A. C. P. Committee on Pan American Conference. Took him with Dr. Powers to meet Dr. Kelchner, head of the Division of International Conferences at the State Department where the preliminaries for arranging a Pan American Conference on Pharmacy were thoroughly explored. Following luncheon at the Roger Smith Hotel, a final conference on the subject at Headquarters, and it looks as though we are on our way toward some worth-while program as part of the Good Neighbor policy.

—12th—

A visit from Dr. Jean Mabileau of the French Public Health Mission for the discussion of future cooperation between French and American pharmacists, and then to lunch with George Hammill at the Roger Smith, where many phases of the surplus property program were discussed. Also, this being Lincoln's birthday it was well to recall amid the tumult and shouting of postwar that we have fought so "Government of the people, by the people and for the people shall not perish from the earth."

—13th—

Early to the office to dispose of routine mail, and then joined Dr. Powers on the way to New York, where he will attend Contact Committee and U. S. P. meetings for the balance of the week. Alighted at Trenton to meet with the New Jersey State Board of Health before which appeared one delegation to advocate compulsory enrichment of flour within the state, and others to settle disputes on the routing of sewage disposal facilities. Later to confer with Pharmacy Board Secretary Powers on problems involving issuance of pharmacy permits to firms with questionable qualifications, and then back to Washington.

—14th—

All day at the routine grind and preparations for the meeting of the Committee on Status of Pharmacists in the Government Service at Headquarters tomorrow. To dinner at the Washington with McCartney, DuMez, Swain and Kendig, all here for tomorrow's meeting and for the preliminary session tonight in which Congressman Durham, George Frates and Arthur Einbeck joined.

—15th—

Attending the meeting of the Committee on Status of Pharmacists in the Government Service in the reading room of the Headquarters Building with Swain, Frates, DuMez, D. B. R. Johnson, H. S. Johnson, Rogers, McCartney, Einbeck and Kendig in attendance and Dargavel, Lusby, Winne and Bohrer absent. Promptly at 11 a. m. came Surgeon-General Kirk and staff to join the meeting and confer on problems of pharmacy in the Army [outlined on page 155]. It was an historic occasion, well worth the efforts of both groups, and should lead to

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a much better understanding of the fundamentals as well as the details of the problem. After a brief session at the office to dispose of the mail and other routine, to dinner with DuMez, Rogers and D. B. R. Johnson at the Madrillon, followed by long discussions of this and that at the hotel.

—16th—

Most of the morning carrying out instructions of the Committee on Status of Pharmacists in the Government Service arrived at the day before, and then accompanied by Dean Rogers to spend the week end at Red Bank.

—18th—

The heavy Monday morning routine and disposal of mail interrupted by emergency calls from Richmond, Va., where help was needed on pending legislation to provide for the addition of a pharmacist to the State Board of Health, and Pat Costello's summary on this subject in the last Proceedings of the N. A. B. P. arrived just in time to be of considerable use.

—19th—

To luncheon with Drs. H. Van Zile Hyde and L. L. Williams, discussing many details of pharmaceutical implications and international drug standards in connection with the proposed International Health Conference of U. N. O. Among the visitors a call from Lt. Catherine Simon, about to leave the Waves to sail into a pharmaceutical career with some manufacturing firm. To dinner at the Statler with P. D.'s Homer Fritch, leaving with a better idea of many problems now engaging manufacturers, especially in the field of antibiotics.

—20th—

Among the long distance calls came one from Russell Rothrock of Indiana citing Hoosier needs for registered pharmacists now whiling away precious hours in the Navy. To lunch with Bob Gasen, now of Bristol Laboratories, and at night to the Press Club for dinner with Wallace Werble, discussing many current problems and listening to his ideas about the effect of traffic in sales outlets other than pharmacies on distribution of drugs through pharmacies.

—22nd—

On this birthday of George Washington with the office closed, there was opportunity to catch up on some routine before leaving at 1 p. m. for Philadelphia to join in the 125th anniversary celebration of the founding of the oldest college of pharmacy in the United States, and there were Beal, Urdang, Griffith, Cook, Kramer, Sappia, Ulan, Dean Crawford and others with whom to converse. Between the afternoon exercises, at which Urdang received the honorary Sc.D. and spoke on the Quaker influence on science, and the dinner at 6:30 a long conference with Chairman Beal of the Council on pending problems.

—25th—

Much routine business at the office, including the designing of a new Life Membership certificate.

—26th—

At last some action on the final preparation of a storeroom for supplies with perpetual inventory arrangements. In the afternoon came Emeritus President Elliott of Purdue to discuss the survey of pharmacy and pharmaceutical education to be undertaken by the American Council on Education, and it is always a pleasure to attempt to educate the educated with respect to pharmacy because the ramifications of drug manufacture and distribution are always fascinating to men in other walks of life. At dinner with J. J. Clarke of United Drug and Liggett, and much conversation on the drug surplus situation.

—27th—

And now the painters actively applying a first coat to each office in this handsome building, with some inconvenience but noting with pleasure what a coat of paint can do to walls and ceilings grown dark with the years. All the afternoon with Einbeck, DuMez and Frates of the Pharmacy Corps Steering Committee composing a communication to the Surgeon-General and getting it into the mill to the committee at large for approval. Distressed to receive a wire announcing death of E. R. Outcalt, deputy secretary of the N. J. State Board of Health, who carried the load of the Department to a greater extent than generally known, thereby hastening his end at fifty-two, which gives one pause.

—28th—

A full staff meeting this afternoon to explain many new developments in the ASSOCIATION'S activities and ask continued cooperation in the very difficult days ahead. Later a visit from J. S. Mordell to discuss surplus property problems as handled by the U. S. Public Health Service for institutions engaged in health activities and so another month completed.

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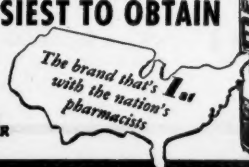

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